Management of Parkinson’s disease

Professor C E Clarke

University of Birmingham
Management of Parkinson’s disease

- When should treatment be started?
  - Early Parkinson’s disease
  - Later Parkinson’s disease
  - Advanced Parkinson’s disease with severe motor complications
- Nursing and allied health interventions
- The future
When should treatment be started?
Recent disease modifying trials in PD

- Failed
  - Co-enzyme Q10
  - Creatine
  - Pramipexole
  - GDNF
  - Foetal transplants (unregulated DA production)

- Going through to larger trials
  - Exenatide
  - Anti-alpha synuclein therapies
Alpha-synuclein

- Major constituent of Lewy body
- Found in a genetic form of Parkinson’s disease
  - PARK1 – chromosome 4q21
  - Triplication worse progression than duplication, so dose of gene (i.e. α-synuclein) important
- Possibly integrate presynaptic signalling and membrane trafficking
Braak hypothesis
Lewy bodies in PD transplants

Figure 4. Host-to-graft spreading of Lewy body pathology in a patient with Parkinson's disease. This patient received a transplant of fetal human mesencephalic dopaminergic neurons into the putamen 16 years previously. Immunohistochemistry for α-synuclein visualizes Lewy bodies and Lewy neurites in (a) the host substantia nigra and (b, c) the transplant. Scale bars, 40 μm. Adapted, with permission, from Ref. [86].

TINS 2010;33:317
Is PD a prion-like disorder?

New treatment

TINS 2010;33:317
When should treatment be started?

- No clear disease modifying treatment
- Major problems with trial designs
- Conclusion
  - Wait for significant functional disability then start symptomatic therapy

Movement Disorders 2008;23:784
Movement Disorders 2011;26:1187
Early Parkinson’s disease
## NICE guideline update 2017

<table>
<thead>
<tr>
<th></th>
<th>Levodopa</th>
<th>Dopamine agonists</th>
<th>MAO-B inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor symptoms</strong></td>
<td>More improvement in motor symptoms</td>
<td>Less improvement in motor symptoms</td>
<td>Less improvement in motor symptoms</td>
</tr>
<tr>
<td><strong>Activities of daily living</strong></td>
<td>More improvement in activities of daily living</td>
<td>Less improvement in activities of daily living</td>
<td>Less improvement in activities of daily living</td>
</tr>
<tr>
<td><strong>Motor complications</strong></td>
<td>More motor complications</td>
<td>Fewer motor complications</td>
<td>Fewer motor complications</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Fewer specified adverse events*</td>
<td>More specified adverse events*</td>
<td>Fewer specified adverse events*</td>
</tr>
</tbody>
</table>
Levodopa-induced motor complications

- Abnormal involuntary movements (dyskinesia)
  - Athetosis
  - Dystonia
- Motor fluctuations
  - Wearing off (end-of-dose deterioration)
  - Unpredictable on/off fluctuations
Dopamine agonists

Delay onset of dyskinesias

N Eng J Med 2000; 342: 1484-1491

Cochrane Database SR 2008
Dopamine agonists
Motor symptoms less well treated

UPDRS part II: Activities of daily living
Mean (2SE) score (all patients)

PD MED EARLY

Design

Early disease = newly diagnosed or less than 6 months PD medication

Randomisation

DA (± LD)  MAOBI* (± LD)  LD* alone

* optional arms
Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson’s disease (PD MED): a large, open-label, pragmatic randomised trial

PD MED Collaborative Group*

Summary
Background Whether initial treatment for Parkinson’s disease should consist of levodopa, dopamine agonists, or monoamine oxidase type B inhibitors (MAOBI) is uncertain. We aimed to establish which of these three classes of drug, as initial treatment, provides the most effective long-term control of symptoms and best quality of life for people with early Parkinson’s disease.

Methods In this pragmatic, open-label randomised trial, patients newly diagnosed with Parkinson’s disease were randomly assigned (by telephone call to a central office; 1:1) between levodopa-sparing therapy (dopamine agonists or MAOBI) and levodopa alone. Patients and investigators were not masked to group assignment. Primary outcomes were the mobility dimension on the 39-item patient-rated Parkinson’s disease questionnaire (PDQ-39) quality-of-life scale (range 0–100 with six points defined as the minimally important difference) and cost-effectiveness. Analysis was intention to treat. This trial is registered, number ISRCTN69812316.

Findings Between Nov 9, 2000, and Dec 22, 2009, 1620 patients were assigned to study groups (528 to levodopa, 632 to dopamine agonist, 460 to MAOBI). With 3-year median follow-up, PDQ-39 mobility scores averaged 1·8 points (95% CI 0·5–3·0, p=0·005) better in patients randomly assigned to levodopa than those assigned to levodopa-sparing therapy, with no increase or attrition of benefit during 7 years’ observation. PDQ-39 mobility scores were 1·4 points (95% CI 0·0–2·9, p=0·05) better in patients allocated MAOBI than in those allocated dopamine agonists. EQ-5D utility scores averaged 0·03 (95% CI 0·01–0·05; p=0·0002) better with levodopa than with levodopa-sparing therapy; rates of dementia (hazard ratio [HR] 0·81, 95% CI 0·61–1·08, p=0·14), admissions to institutions (0·86, 0·63–1·18; p=0·4), and death (0·85, 0·69–1·06; p=0·17) were not significantly different, but the upper CIs precluded any substantial increase with levodopa compared with levodopa-sparing therapy. 179 (28%) of 632 patients allocated dopamine agonists and 104 (23%) of 460 patients allocated MAOBI discontinued allocated treatment because of side-effects compared with 11 (2%) of 528 patients allocated levodopa (p<0·0001).

Interpretation Very small but persistent benefits are shown for patient-rated mobility scores when treatment is initiated with levodopa compared with levodopa-sparing therapy. MAOBI as initial levodopa-sparing therapy was at least as effective as dopamine agonists.

Funding UK National Institute for Health Research Health Technology Assessment Programme and UK Department of Health.
LD versus LD-sparing therapy

PDQ-39 mobility

Test for increasing difference over time: p=0.2

Average difference (favours LD): 1.8 points (CI: 0.6 to 3.0); p=0.004

The Lancet 2014; DOI 10.1016/S0140-6736(14)60683-8
LD versus LD-sparing therapy

Dyskinesia onset

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>LD</td>
<td>528</td>
<td>109</td>
<td>86.6</td>
</tr>
<tr>
<td>LD-Sparing</td>
<td>878</td>
<td>121</td>
<td>143.4</td>
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</table>

\[2P = 0.003\]

At risk:

<table>
<thead>
<tr>
<th></th>
<th>LD</th>
<th>LD-Sparing</th>
</tr>
</thead>
<tbody>
<tr>
<td>528</td>
<td>454</td>
<td>764</td>
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<tr>
<td>455</td>
<td>355</td>
<td>630</td>
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<tr>
<td>258</td>
<td>465</td>
<td>320</td>
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<td>129</td>
<td>208</td>
<td>123</td>
</tr>
<tr>
<td>78</td>
<td>46</td>
<td>57</td>
</tr>
</tbody>
</table>
Is treatment effect different according to age?

No evidence that treatment effect differs across age subgroups, p=0.8
NICE guideline update 2017

- “In … PD MED … there were long-term quality of life gains associated with initial levodopa therapy (which included the long-term disutility of dyskinesia), implying that for this population the balance of benefits and harms favours initial treatment with levodopa.”

- “Offer levodopa to people in the early stages of Parkinson’s disease whose motor symptoms impact on their quality of life”
Early Parkinson’s disease

- Commence levodopa preparation
- Co-careldopa 25/100 strength TDS with meals
- With disease progression, titrate up dose
- Co-careldopa 25/100 strength x 5 daily (doses with mid-morning and mid-afternoon drinks)
- Then co-careldopa 25/100 strength x 6 daily (double dose with breakfast)
- Maximum = 8-9 mg/kg body weight

Fahn et al. ELLDOPA trial. NEJM 2004;351:2498
Sharma et al. Park Rel Disord 2010;16:490
‘Rational polypharmacy’ in PD

- Levodopa
- Restrict levodopa dose to ~ 600 mg/d
Later Parkinson’s disease
# NICE guideline update 2017

<table>
<thead>
<tr>
<th>Category</th>
<th>Dopamine agonists</th>
<th>MAO-B inhibitors</th>
<th>COMT inhibitors</th>
<th>Amantadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor symptoms</td>
<td>Improvement in motor symptoms</td>
<td>Improvement in motor symptoms</td>
<td>Improvement in motor symptoms</td>
<td>No evidence of improvement in motor symptoms</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>Improvement in activities of daily living</td>
<td>Improvement in activities of daily living</td>
<td>Improvement in activities of daily living</td>
<td>No evidence of improvement in activities of daily living</td>
</tr>
<tr>
<td>Off time</td>
<td>More off-time reduction</td>
<td>Off-time reduction</td>
<td>Off-time reduction</td>
<td>No studies reporting this outcome</td>
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<tr>
<td>Adverse events</td>
<td>Intermediate risk of adverse events</td>
<td>Fewer adverse events</td>
<td>More adverse events</td>
<td>No studies reporting this outcome</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>More risk of hallucinations</td>
<td>Lower risk of hallucinations</td>
<td>Lower risk of hallucinations</td>
<td>No studies reporting this outcome</td>
</tr>
</tbody>
</table>
Adjuvant placebo-controlled trials meta-analysis

- Dopamine agonists and tolcapone superior to entacapone and rasagiline in:
  - Reducing off time
  - Reducing levodopa dose
  - Without disproportionately increasing dyskinesia and dopaminergic adverse events

*Cochrane Database Syst Rev. 2010(7):CD007166
Mov Disord 2011;26:587*
Later disease = patients with motor complications uncontrolled by current PD medication

Randomisation

COMTI (± LD)  MAOBI* (± LD)  DA* (± LD)

* optional arms
Time to stopping drugs in randomised class

% Stopping Randomised Treatment

Years from Randomisation

At risk:

<table>
<thead>
<tr>
<th></th>
<th>DA</th>
<th>MAOBI</th>
<th>COMTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>144</td>
<td>146</td>
<td>210</td>
</tr>
<tr>
<td>Obs.</td>
<td>70</td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>Exp.</td>
<td>73.2</td>
<td>67.8</td>
<td>99.0</td>
</tr>
</tbody>
</table>

2P = 0.3
MAOBI versus COMTI

PDQ-39 mobility

Test for increasing difference over time: p=0.01

Slopes diverging at rate of 1.2 points per year (0.3 to 2.1) (favours MAOBI)
‘Rational polypharmacy’ in PD

- Levodopa
- Restrict levodopa dose to ~ 600 mg/d
- Add selegiline (rasagiline if not tolerated)
- Add dopamine agonist (once daily prep)
- Add entacapone or opicapone
‘New’ overtreatment disorders

- Impulse control disorders
  - Pathological gambling
  - Hypersexuality
  - Punding = repetitive stereotyped motor acts (e.g. collecting and categorising things)
  - Weintraub et al, DOMINION study, n=3090 - 14%

- Dopamine dysregulation syndrome
  - Drug hoarding, overdosing (abuse)
  - Related to drug or personality

- Overlap between two conditions

*Arch Neurol* 2010;67:589
Advanced Parkinson’s disease with severe motor complications
Amantadine

- Anti-dyskinetic effect in 4 RCTs in only 93 patients
- 100 mg/d titrated up weekly by 100 mg to 100 mg tds
- S/E psychosis and livedo reticularis
Subcutaneous apomorphine injections and infusions
Subthalamic deep brain stimulation
UK PD SURG Trial

RCT of STN DBS v delay surgery to end of waiting list (~12 months)

Closed recruitment 31-12-06

N = 366

Baseline to 12 month change:

- PDQ 39 Summary Index = -5.4 v +0.3 (p=0.0003)
- PDQ 39 Mobility = -8.9 v +0.9 (p=0.002)
- PDQ 39 ADL = -12.2 v +0.4 (<0.0001)

*Lancet Neurol 2010;9:581*
Intrajejunal levodopa gel infusion (Duodopa®)
‘Rational polypharmacy’ in PD

- Levodopa
- Restrict levodopa dose to ~ 600 mg/d
- Add selegiline (rasagiline if not tolerated)
- Add dopamine agonist (once daily prep)
- Add entacapone (Stalevo®) or opicapone
- Add intermittent sc apomorphine
- Consider continuous apomorphine infusion
- Consider surgery
- Consider Duodopa®
Parkinson’s Disease
Nurse Specialists
RCT of Parkinson’s Disease Nurse Specialists

- 9 randomly selected health authority areas in UK stratified for mortality and deprivation
- 438 GPs participated (863 approached)
- 1041 randomised to Parkinson’s disease nurse and 818 to control group
- Interviewed at home by blinded observers QoL scales and cost-benefit analysis
- No effect on QoL but cost neutral

*BMJ 2002;324:1072-5*
Physiotherapy, occupational therapy, speech and language therapy
### UPDRS motor score

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention</th>
<th>No Intervention</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>4.16.1 General Physiotherapy v Control</td>
<td>Chandler 1999</td>
<td>-1</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Ellis 2005</td>
<td>-3</td>
<td>6.6</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Fisher 2008</td>
<td>-3.8</td>
<td>8.17</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 2.79 (P = 0.005)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.16.2 Exercise v Control</td>
<td>Sage 2009a</td>
<td>-3.7</td>
<td>6.72</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 2.08 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.16.3 Treadmill v Control</td>
<td>Fisher 2008</td>
<td>-2.8</td>
<td>9.72</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>10</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Test for overall effect: Z = 0.02 (P = 0.98)</td>
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<tr>
<td>4.16.4 Cueing v Control</td>
<td>de Bruin 2010a</td>
<td>-5.6</td>
<td>9.17</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Shankar 2008</td>
<td>-4</td>
<td>8.29</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>25</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%</td>
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<tr>
<td></td>
<td>Test for overall effect: Z = 2.03 (P = 0.04)</td>
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<td></td>
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<tr>
<td>4.16.5 Dance v Control</td>
<td>Earhart 2010</td>
<td>-5.4</td>
<td>11.9</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Hackney 2009</td>
<td>-2.1</td>
<td>10.96</td>
<td>31</td>
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<td></td>
<td>Subtotal (95% CI)</td>
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<td>Heterogeneity: Chi² = 0.16, df = 1 (P = 0.68); I² = 0%</td>
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<td>Test for overall effect: Z = 2.78 (P = 0.005)</td>
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<tr>
<td>4.16.6 Martial Arts v Control</td>
<td>Hackney 2009</td>
<td>-1.5</td>
<td>6.6</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Schmitz-Hubsch 2006</td>
<td>-0.32</td>
<td>10.9</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 2.87 (P = 0.004)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Total (95% CI)</td>
<td>235</td>
<td></td>
<td></td>
</tr>
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</table>

Test for subgroup differences: Chi² = 3.61, df = 5 (P = 0.61), I² = 0%
## 5.17.1 General Physiotherapy v Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>No Intervention</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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</thead>
<tbody>
<tr>
<td>Chandler 1999</td>
<td>4</td>
<td>14.94</td>
<td>26</td>
<td>3.32</td>
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<tr>
<td>Subtotal</td>
<td>95% CI</td>
<td>26</td>
<td>26</td>
<td>9.4%</td>
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</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

## 5.17.2 Exercise v Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>No Intervention</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen 2010</td>
<td>-1</td>
<td>14.3</td>
<td>21</td>
<td>4.9</td>
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<tr>
<td>Klassen 2007</td>
<td>0.25</td>
<td>4.06</td>
<td>17</td>
<td>-1</td>
</tr>
<tr>
<td>Meek 2010</td>
<td>-2.6</td>
<td>15.6</td>
<td>19</td>
<td>-3.1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>95% CI</td>
<td>57</td>
<td>47</td>
<td>30.9%</td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 1.12, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

## 5.17.3 Cueing v Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>No Intervention</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nieuwboer 2007</td>
<td>-3.42</td>
<td>11.08</td>
<td>76</td>
<td>-1.84</td>
</tr>
<tr>
<td>Subtotal</td>
<td>95% CI</td>
<td>76</td>
<td>77</td>
<td>35.6%</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)

## 5.17.4 Dance v Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>No Intervention</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackney 2009</td>
<td>-3.84</td>
<td>5.4</td>
<td>31</td>
<td>-1.5</td>
</tr>
<tr>
<td>Subtotal</td>
<td>95% CI</td>
<td>31</td>
<td>17</td>
<td>12.7%</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

## 5.17.5 Martial Arts v Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>No Intervention</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackney 2009</td>
<td>1.55</td>
<td>5.37</td>
<td>13</td>
<td>-1.5</td>
</tr>
<tr>
<td>Subtotal</td>
<td>95% CI</td>
<td>13</td>
<td>17</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)

Total | 95% CI | 203 | 184 | 100.0% | -0.35 [-2.66, 1.96] |

Heterogeneity: Ch² = 2.99, df = 6 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Ch² = 1.87, df = 4 (P = 0.76), I² = 0%

BMJ 2012;345: doi: 10.1136/bmj.e5004
Physiotherapy and Occupational Therapy vs No Therapy in Mild to Moderate Parkinson Disease
A Randomized Clinical Trial

Carl E. Clarke, MD, Smitas Patel, Mic, Natalie Ives, MSc, Caroline C. Rick, PhD, Trudy Dowling, DSc, Rebecca Winson, MSc, Keith Wheatley, DPhil, Marian E. Walker, PhD, Catharina M. Sackley, PhD
for the PD REHAB Collaborative Group

IMPORTANCE It is unclear whether physiotherapy and occupational therapy are clinically effective and cost-effective in Parkinson disease (PD).

OBJECTIVE To perform a large pragmatic randomized clinical trial to evaluate the clinical effectiveness of individualized physiotherapy and occupational therapy in PD.

DESIGN, SETTING, AND PARTICIPANTS The PD REHAB Trial was a multicenter, open-label, parallel group, controlled efficacy trial. A total of 762 patients with mild to moderate PD were recruited from 38 sites across the United Kingdom. Recruitment took place between October 2009 and June 2012, with 15 months of follow-up.

INTERVENTIONS Participants with limitations in activities of daily living (ADL) were randomized to physiotherapy and occupational therapy or no therapy.

MAIN OUTCOMES AND MEASURES The primary outcome was the Nottingham Extended Activities of Daily Living (NEADL) Scale score at 3 months after randomization. Secondary outcomes were health-related quality of life (assessed by Parkinson Disease Questionnaire-39 and EuroQol-5D); adverse events; and caregiver quality of life. Outcomes were assessed before trial entry and then 3, 9, and 15 months after randomization.

RESULTS Of the 762 patients included in the study (mean [SD] age, 70 [9] years), 381 received physiotherapy and occupational therapy and 381 received no therapy. At 3 months, there was no difference between groups in NEADL total score (difference, 0.5 points; 95% CI, −0.7 to 1.7; P = .41) or Parkinson Disease Questionnaire-39 summary index (0.007 points; 95% CI, −1.5 to 1.5; P = .99). The EuroQol-5D quotient was of borderline significance in favor of therapy (−0.03, 95% CI, −0.07 to −0.002; P = .04). The median therapist contact time was 4 visits of 38 minutes over 8 weeks. Repeated measures analysis showed no difference in NEADL total score, but Parkinson Disease Questionnaire-39 summary index (diverging 1.6 points per annum; 95% CI, 0.47 to 2.62; P = .005) and EuroQol-5D score (0.02, 95% CI, 0.0007 to 0.03; P = .04) showed small differences in favor of therapy. There was no difference in adverse events.

CONCLUSIONS AND RELEVANCE Physiotherapy and occupational therapy were not associated with immediate or medium-term clinically meaningful improvements in ADL or quality of life in mild to moderate PD. This evidence does not support the use of low-dose, patient-centered, goal-directed physiotherapy and occupational therapy in patients in the early stages of PD. Future research should explore the development and testing of more structured and intensive physical and occupational therapy programs in patients with all stages of PD.

TRIAL REGISTRATION srcrn.org/trial: ISRCTN14452402

JAMA Neurol. doi:10.1001/jamaneurol.2015.4452
Published online January 19, 2016.
PD REHAB Trial

- HTA Programme funded (£1.6 million)
- Randomised controlled trial to assess the clinical- and cost-effectiveness of physiotherapy and occupational therapy in Parkinson's disease versus no therapy
- Recruited 763 patients from 37 neurology & geriatrics units over 3 years (6-10 patients per annum)
- Primary outcomes at 3 months - NEADL; PDQ 39
- No benefit in mild-moderate PD
NICE guideline update 2017

- “Consider referring patients with early PD to physiotherapists and occupational therapists with experience in treating Parkinson's disease”
- “Offer PD patients with balance or motor function problems physiotherapy and occupational therapy”
- Watch for PD SAFE trial results!
PD COMM Trial

- Dunhill funding for pilot trial
- Randomised controlled trial to assess the clinical- and cost-effectiveness of Lee Silverman Voice Therapy versus NHS SLT versus no treatment for speech problems in PD
- Pilot planned n=60; 5 centres over 2 years
- Outcomes include Intelligibility (self-reported Voice Handicap Index)
- Recruited 89 patients from 11 centres
- Now recruiting to HTA Programme funded nationwide trial
## Results – Voice Handicap Index

<table>
<thead>
<tr>
<th>LSVT</th>
<th>NHS</th>
<th>Control</th>
<th>LSVT v control</th>
<th>NHS v control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=22</td>
<td>N=22</td>
<td>N=28</td>
<td>-12.5 (SE=6.8)</td>
<td>-9.8 (SE=6.7)</td>
</tr>
<tr>
<td>33.5</td>
<td>36.2</td>
<td>46.0 (25.1)</td>
<td>95% CI: -26.2 to 1.2</td>
<td>95% CI: -23.2 to 3.6</td>
</tr>
<tr>
<td>(22.36)</td>
<td>(21.18)</td>
<td></td>
<td>P=0.07</td>
<td>P=0.1</td>
</tr>
</tbody>
</table>
Non-motor features of PD

- Mental health - dementia, depression, psychosis (hallucinations, delusions)
- Autonomic - constipation, low blood pressure (orthostatic hypotension), swallowing difficulty (dysphagia)
- Sleep disturbance
- Pain - frozen shoulder, co-morbid arthritis
The future
The future

- Disease modifying therapy
  - Halting alpha synuclein spread may be neuroprotective (a ‘cure’)
  - May be more effective than seeking new symptomatic therapies
- Better treatments for non-motor features
- More consideration of end of life issues, including hospitalisation
### More consideration of end of life issues

**Study or sub-category** | **Parkinson's disease nN** | **Control nN** | **OR (fixed) 95% CI** | **Weight %** | **OR (fixed) 95% CI**
--- | --- | --- | --- | --- | ---

**01 Hypothesis generating report**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Parkinson's disease nN</th>
<th>Control nN</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outhwaite 2001</td>
<td>15304</td>
<td>30608</td>
<td>2.52 [2.42, 2.63]</td>
<td>93.44</td>
<td>2.52 [2.42, 2.63]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 7779 (Parkinson's disease), 8899 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable

Test for overall effect: $Z = 45.14$ ($P < 0.00001$)

**02 Case-control studies**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Parkinson's disease nN</th>
<th>Control nN</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebenezer 1990</td>
<td>116/243</td>
<td>46/190</td>
<td>2.66 [1.75, 4.05]</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Ben-Shlomo 1985</td>
<td>195/220</td>
<td>295/421</td>
<td>3.33 [2.09, 5.31]</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Bennett 1996</td>
<td>124/159</td>
<td>146/301</td>
<td>3.76 [2.43, 5.83]</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Tison 1998</td>
<td>16/24</td>
<td>605/2768</td>
<td>7.15 [3.05, 16.79]</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Chen 2001</td>
<td>21/52</td>
<td>1205/9957</td>
<td>8.59 [3.89, 18.79]</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>Elbaz 2003</td>
<td>110/196</td>
<td>79/185</td>
<td>1.72 [1.14, 2.57]</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Fall 2003</td>
<td>121/170</td>
<td>229/510</td>
<td>3.03 [2.09, 4.41]</td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td>Hughes 2004</td>
<td>50/90</td>
<td>13/50</td>
<td>3.56 [1.67, 7.58]</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>De Luca 2005</td>
<td>90/166</td>
<td>1623/6803</td>
<td>5.04 [2.87, 7.79]</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>D'Amelio 2006</td>
<td>46/58</td>
<td>70/116</td>
<td>2.52 [1.21, 5.26]</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1378</td>
<td>21291</td>
<td>3.13 [2.70, 3.62]</td>
<td>6.56</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 17.78$, df = 9 ($P = 0.04$), $\phi = 49.4\%$

Test for overall effect: $Z = 15.25$ ($P < 0.00001$)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Parkinson's disease nN</th>
<th>Control nN</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>16682</td>
<td>51899</td>
<td>2.56 [2.46, 2.66]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 26.90$, df = 10 ($P = 0.003$), $\phi = 62.8\%$

Test for overall effect: $Z = 47.62$ ($P < 0.00001$)

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*J Neurol 2010; 257 (suppl 2):S262*
Management of Parkinson’s disease

- When should treatment be started?
- Early Parkinson’s disease
- Later Parkinson’s disease
- Advanced Parkinson’s disease with severe motor complications
- Nursing and allied health interventions
- The future