Original Investigation

Physiotherapy and Occupational Therapy vs No Therapy in Mild to Moderate Parkinson Disease
A Randomized Clinical Trial

Carl E. Clarke, MD; Smitaa Patel, MSc; Natalie Ives, MSc; Caroline E. Rick, PhD; Francis Dowling, BSc; Rebecca Woolley, MSc; Keith Wheatley, DPhil; Marion F. Walker, PhD; Catherine 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 [9.1] 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 58 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, 0.00007 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.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A list of the PD REHAB Collaborative Group members is at the end of the article.

Corresponding Author: Carl E. Clarke, MD, Department of Neurology, Sandwell and West Birmingham Hospitals National Health Service Trust, City Hospital, Dudley Road, Birmingham B18 7QH, England (carlclarke@nhs.net).

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Parkinson disease (PD) causes problems with activities of daily living (ADL) that are only partially treated by medication and occasionally surgery. Despite treatment, patients go on to develop intractable motor problems, including falls, with mental health problems and other nonmotor symptoms. Physiotherapy (PT) and occupational therapy (OT) are traditionally used later in the disease.[1] However, service provision varies widely, with some centers involving physiotherapists and occupational therapists from diagnosis, while other areas have no specialist services.

Cochrane reviews of PT for PD found small but significant effects on motor function but not quality of life (QoL).[2,3] A Cochrane review of OT found insufficient evidence of effectiveness.[4] Previous trials with both therapies were small with short-term follow-up.[2-4] Despite this lack of evidence, the UK National Institute for Health and Care Effectiveness guidelines, although recognizing these shortcomings and recommending further trials, stated that all patients should have access to both therapies.[1]

The PD REHAB Trial was designed to evaluate the clinical effectiveness and cost-effectiveness of individualized PT and OT in patients with PD. The current trial design was informed by our pilot study of OT in PD.[5]

Key Points

Question: Are physiotherapy and occupational therapy clinically effective in Parkinson disease?

Findings: In this randomized clinical trial in 762 patients with mild to moderate Parkinson disease, physiotherapy and occupational therapy were not associated with immediate or medium-term clinically meaningful improvements in activities of daily living or quality of life.

Meaning: This study shows that more structured and intensive physical and occupational therapy programs should be developed and tested at all stages of Parkinson disease.

Methods

The PD REHAB Trial was a large-scale pragmatic, multicenter, randomized clinical trial to evaluate the effects of individualized PT and OT on ADL and QoL in patients with PD. The full trial protocol can be found in Supplement 1.

Study Participants

Recruitment took place between October 2009 and June 2012. Patients from 38 neurology or geriatric medicine outpatient centers across the United Kingdom were invited to take part. Eligibility criteria were idiopathic PD defined by UK Parkinson Disease Society Brain Bank Criteria[6]; self- or caregiver-reported limitations in ADL; and the investigator was uncertain that the patient would require PT and/or OT during the 15 months of the trial (ie, equipoise about the need for therapy existed). Exclusion criteria were dementia as locally defined and receipt of PT or OT for PD in the last 12 months. All patients gave written informed consent before randomization. Ethical approval was granted by the West Midlands Research Ethics Committee and local approval was obtained at each participating center.

Randomization and Therapy Allocation

Patients were randomized (1:1) between combined PT and OT (therapies group) or no therapy (control group) using an online randomization service at the University of Birmingham Clinical Trials Unit. Randomization used a computer-based algorithm with minimization by baseline Nottingham Extended Activities of Daily Living (NEADL) Scale total score (limitations in ADL: severe, 0-21; moderate, 22-43; and mild 44-66), Hoehn and Yahr (H&Y) stage[7] (≤2; 2.5; 3; and ≥4), and age (<60; 60-69; 70-79; and ≥80 years).

Intervention

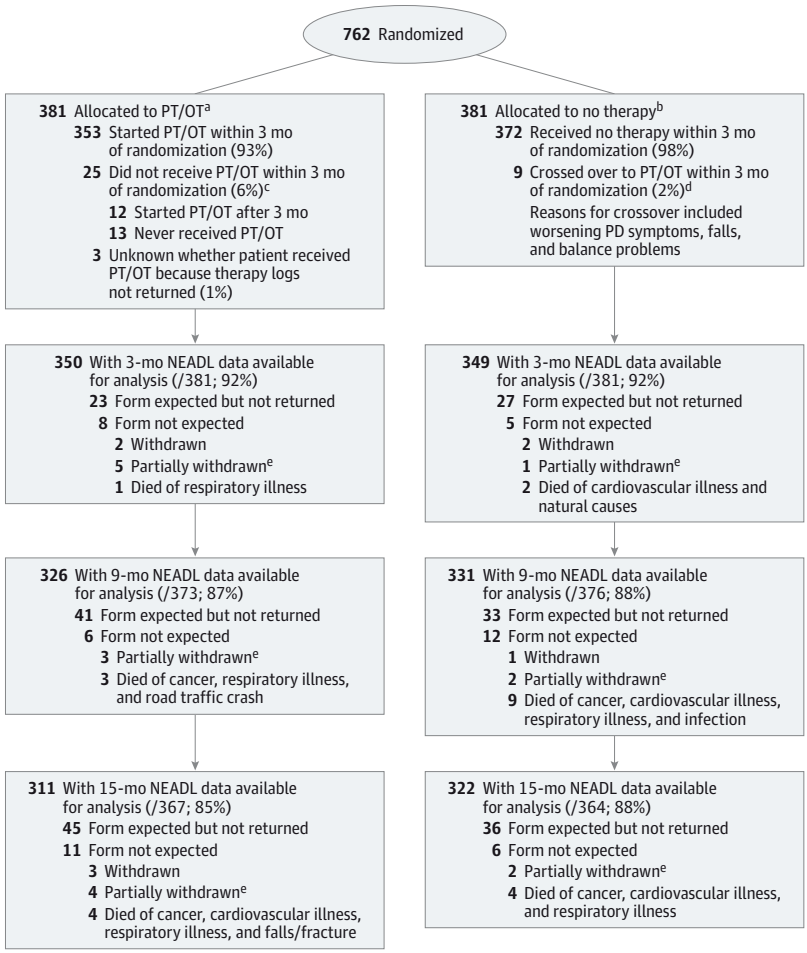
Physiotherapy and OT were delivered in the community and/or outpatient setting by qualified therapists working within the National Health Service (NHS) per local practice. Before the trial, a framework for therapy content was developed and agreed on by expert therapist groups based on previous work on standards of NHS PT and OT and European guidelines.[8-11] This framework was based on usual NHS practice and not an innovative intervention. Following initial assessments by both therapists, therapy was tailored to an individual patient's requirements using a patient-centered joint goal-setting approach. Interactions between therapists and patients were described and quantified using predefined recording forms and included administration time (eg, ordering equipment). Control patients consented to have therapies deferred until the end of the 15-month trial, unless pressing reasons for therapy developed. Because therapies may have been arranged outside the trial, control patients were asked whether they had received any therapy at each assessment point.

Primary Outcome Measure

Total NEADL score at 3 months after randomization was the primary outcome measure.[12] The NEADL measures instrumental ADL, which are specifically addressed by PT and OT and includes more complex ADL issues such as making a meal, cleaning, and traveling on public transport. The NEADL scale was developed for stroke but is used widely as a generic outcome measure in rehabilitation trials of older people. It is sensitive to change in OT trials[13] and was successfully used in our pilot study of OT for PD, with good correlation with the Unified Parkinson Disease Rating Scale and the Parkinson Disease Questionnaire-39 (PDQ-39) ADL domains.[5]

Secondary outcome measures were patient-rated QoL using the 39-item PDQ,[14] consisting of 8 domains and the most widely used disease-specific QoL rating scale for PD, and EuroQol-5D (EQ-5D, 3-level version), a generic QoL scale; adverse events; and caregiver well-being using Short Form-12 (SF-12, version 2). Following a risk assessment, only therapy-related adverse events and serious adverse events were recorded. These were defined as falls or equipment failure leading to injury requiring a hospital, general practitioner, or ambulance visit or to death. A health economics analysis was conducted alongside PD REHAB and will be reported separately. Outcomes were collected in person at baseline before randomization, then by mail at 3, 9,

Figure 1. CONSORT Diagram for PD REHAB Trial



Patient recruitment and follow-up. Numbers of patients assessed for eligibility and excluded are not included in the flow diagram because screening logs are not available for this trial, so these data cannot be provided. NEADL indicates Nottingham Extended Activities of Daily Living; OT, occupational therapy; PT, physical therapy; PD, Parkinson disease.

[a] Eight patients randomized to the PT and OT group were later found to be ineligible because they had received PT and/or OT for PD in the 12 months prior to randomization (exclusion criteria). One patient did not receive any PT or OT after randomization (crossover; only baseline data available: diagnosed as having cancer and died at 5 months after randomization). One patient did not receive PT or OT within 3 months but was referred for PT outside of the trial at 6 months (3-, 9-, and 15-month data available). The other 6 patients all received PT and/or OT after randomization (baseline and 3-month data available except for 1 patient, where only baseline data were available).

[b] Three patients randomized to the no therapy group were subsequently found to be ineligible because they had received PT and/or OT for PD in the 12 months prior to randomization (exclusion criteria). One patient received PT and/or OT within 3 months of randomization (crossover). For all 3 patients, baseline and 3-month data were available.

[c] Thirteen patients randomized to the PT and OT group are known to have not received any PT or OT. Baseline and 3-month data are available for 2 of these patients (for the other 11 patients, only baseline data are available). Twelve patients did not receive PT or OT by 3 months after randomization but did start therapy after 3 months; baseline and 3-month data are available for all patients (except 2, 1 of whom had baseline data only and 1 who had 3-month data only).

[d] Nine patients randomized to no therapy had some PT and/or OT before their 3-month NEADL form was completed; all patients had baseline and 3-month data available.

[e] Partially withdrawn patients did not want to complete patient forms but agreed to clinical follow-up.

and 15 months after randomization. Antiparkinsonian medication dosage was converted into levodopa dose equivalents using a standard formula.[15]

Statistical Analysis

A minimally clinically important change in NEADL score in patients with stroke is 1 to 2 points.[16] However, such a small change may be of little benefit to patients; a clinically meaningful change in NEADL for patients is likely to be around double this at 2.5 points. A 2-point change in NEADL score represents becoming independent in 1 item (eg, stair climbing and crossing roads) or improvement in 2 items (eg, being dependent on another person with help to being fully independent). To detect a 2.5-point difference in NEADL at 3 months (using the observed SD from the PD OT pilot trial[5] of 10.1 points; $P = .05$, 2-tailed; 90% power) required 340 patients in each group: this increased to 750 participants (375 per group) to allow for around 10% noncompliance and drop out.

Table 1. Demographics and Baseline Characteristics

Characteristic	PT/OT	No Therapy
No. of patients randomized	381	381
Demographics		
Age, mean (SD) [range], y[a]	70 (9.1) [35-90]	70 (9.3) [35-91]
Age category, No. (%), y		
<60	47 (12)	46 (12)
60-69	129 (34)	129 (34)
70-79	148 (39)	151 (40)
≥80	57 (15)	55 (14)
Male, No. (%)	240 (63)	258 (68)
BMI		
No.	327	333
Mean (SD)	27.2 (5.4)	26.9 (4.4)
Range	16.5-54.9	16.8-44.0
Stage of PD		
Duration of PD, y		
No.	381	379
Mean (SD)	4.5 (4.9)	4.6 (4.5)
Range	0.01-29.9	0-25.6
Median (IQR)	3.0 (1.0-6.1)	3.3 (1.3-6.4)
Hoehn & Yahr stage, No. (%)[a]		
≤2.0	254 (67)	254 (67)
2.5	46 (12)	46 (12)
3.0	61 (16)	61 (16)
≥4.0	20 (5)	20 (5)
Drug dose		
Levodopa equivalent dose, mg/d		
No.	381	381
Mean (SD) [range]	453 (357.9)	498 (372.8)
Range	0-1877	0-2181
NEADL Scale[b]		
Total score		
No.	381	381
Mean (SD) [range]	51 (12.9)	51 (13.3)
Range	6-66	8-66
Median (IQR)	53 (43-61)	54 (42-62)
NEADL total score category, No. (%)[a]		
0-21 (severe)	14 (4)	14 (4)
22-43 (moderate)	88 (23)	88 (23)
44-66 (mild)	279 (73)	279 (73)
PDQ-39[c]		
Summary index		
No.	380	377
Mean (SD) [range]	23.8 (14.5)	23.7 (14.4)
Range	2.4-78.4	1.9-67.4
Median (IQR)	22.4 (12.6-32.3)	21.1 (12.2-33.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; NEADL, Nottingham Extended Activities of Daily Living; OT, occupational therapy; PD, Parkinson disease; PDQ-39, Parkinson Disease Questionnaire–39; PT, physical therapy.

[a] Age, Hoehn & Yahr stage, and NEADL total score were minimization variables in the randomization algorithm.

[b] Total score ranges from 0 to 66, where higher scores are better.

[c] Summary index ranges from 0 to 100, where lower scores are better.

The primary analysis was change in NEADL total score in the therapies group between baseline and the 3-month assessment compared with that in the no therapy group. An independent 2-sample *t* test was used to compare changes between baseline and 3 months in the NEADL score between the 2 groups. Results are presented as mean difference between groups with 95% CIs. This analysis was repeated for individual NEADL domains and secondary outcome measures. The medium-term effect or whether any benefit of treatment persisted beyond the initial intervention period was evaluated at 9 and 15 months after randomization, using both *t* tests at each point and a mixed-model repeated-measures analysis across all points for all outcomes.

Analyses were performed on an intention-to-treat basis. Missing data in PDQ-39 domain scores were imputed using an expectation maximization algorithm.[17,18] There is no established imputation method for the NEADL scale; therefore, primary analyses used available data only, with no imputation for missing values. However, sensitivity analyses using a best (score, 3), worst (score, 0), middle (score, 1.5), and average (at participant level) case score for missing items on the NEADL were explored. Three a priori subgroup analyses used a test of interaction to explore the effect of the therapies at 3 months at different levels of ADL, disease stage, and age. All subgroup analyses were interpreted cautiously.

Analyses were performed using SAS version 9.2 (SAS Institute). Interim analyses of unblinded efficacy and safety data were reviewed annually by an independent data monitoring committee, which reported to an independent Trial Steering Committee.

Results

Study Population

A total of 762 people with PD were randomized to either combined PT and OT or no therapy (381 per group; **Figure 1**). Baseline characteristics were similar between groups (**Table 1**). The mean age was 70 years, 65% were male, and the median disease duration was 3.1 years (mean, 4.6 years). Most patients had mild to moderate disease, with 67% in H&Y stage 2 or less (254 patients in each group) and median NEADL total score of 54 (mean, 51).

At 3 months, 92% of patients (350 in the PT/OT arm and 349 in the no therapy arm) in each arm had completed the NEADL (Figure 1). By 15 months, 311 (82% of 381 patients randomized) in the therapies arm had completed the NEADL compared with 322 (85% of 381 patients randomized) in the control arm.

Twenty-five patients (6%) allocated to the therapies arm did not receive therapy by 3 months after randomization (12 started PT and/or OT after 3 months and 13 never received any therapy; Figure 1). Nine patients (2%) allocated to no therapy received therapy for PD-related problems within 3 months, mainly owing to worsening PD symptoms including falls and imbalance (Figure 1).

Therapy Content

In the therapies group, the median number of therapy sessions was 4 (range, 1-21), with a mean time per session of 58 minutes. The mean duration of therapy was 8 weeks. The mean total dose of both therapies was 263 minutes (range, 38-1198

Table 2. Patient Activities of Daily Living and Quality of Life Scores at 3 Months

Variable	Mean (SD)						Mean Difference (95% CI)[a]	*P* Value
	Baseline		3 mo		Mean Change From Baseline			
	PT/OT	No Therapy	PT/OT	No Therapy	PT/OT	No Therapy		
NEADL Scale[b]								
Total score								
No. of patients	381	381	294	304	294	304	0.5 (−0.7 to 1.7)	.41
Score	50.5 (12.9)	50.9 (13.3)	49.6 (14.0)	50.3 (14.5)	−1.5 (7.8)	−1.0 (7.4)		
Mobility								
No. of patients	376	372	338	338	334	330	0.1 (−0.3 to 0.5)	.56
Score	13.9 (4.0)	13.8 (4.2)	13.6 (4.2)	13.6 (4.4)	−0.4 (2.6)	−0.2 (2.4)		
Kitchen activities								
No. of patients	379	373	337	337	335	329	0.005 (−0.3 to 0.3)	.97
Score	13.0 (2.7)	13.0 (2.9)	13.0 (3.0)	12.9 (3.2)	−0.2 (2.2)	−0.2 (1.9)		
Domestic tasks								
No. of patients	374	370	330	332	325	323	0.5 (−0.06 to 1.0)	.08
Score	10.9 (4.2)	11.1 (4.3)	10.4 (4.5)	10.8 (4.4)	−0.8 (3.4)	−0.3 (3.2)		
Leisure activities								
No. of patients	376	365	318	329	316	318	0.01 (−0.4 to 0.4)	.94
Score	12.9 (4.1)	13.0 (4.0)	13.0 (4.1)	13.1 (4.0)	−0.2 (2.4)	−0.1 (2.4)		
PDQ-39[b]								
No.	380	377	349	351	348	347		
Mobility	32.7 (26.1)	31.3 (25.8)	33.2 (27.3)	33.3 (28.0)	1.1 (17.1)	2.6 (15.8)	−1.5 (−3.9 to 1.0)	.23
Activities of daily living	31.3 (23.1)	30.6 (21.8)	32.1 (23.8)	31.5 (23.8)	1.6 (14.3)	1.0 (16.7)	0.7 (−1.7 to 3.0)	.58
Emotional well-being	23.9 (18.5)	23.0 (18.1)	25.9 (19.8)	25.5 (20.3)	2.6 (13.1)	3.0 (16.8)	−0.5 (−2.7 to 1.8)	.68
Stigma	18.3 (22.9)	17.1 (21.0)	19.8 (23.1)	17.6 (21.3)	1.6 (17.7)	0.9 (17.5)	0.7 (−2.0 to 3.3)	.62
Social support	6.6 (14.0)	5.7 (11.0)	10.3 (17.4)	9.3 (15.1)	3.6 (15.6)	3.8 (14.9)	−0.2 (−2.5 to 2.0)	.83
Cognition	26.6 (20.1)	27.3 (21.1)	28.8 (20.6)	29.6 (21.6)	2.2 (16.5)	2.2 (17.0)	−0.05 (−2.6 to 2.4)	.97
Communication	16.5 (18.2)	18.5 (19.8)	20.8 (20.1)	21.8 (21.1)	4.8 (15.7)	3.0 (17.4)	1.8 (−0.7 to 4.2)	.16
Bodily discomfort	34.8 (23.4)	35.9 (24.0)	36.5 (24.4)	38.6 (24.1)	2.0 (20.7)	2.8 (21.1)	−0.8 (−3.9 to 2.3)	.62
Summary index	23.8 (14.5)	23.7 (14.4)	25.9 (16.5)	25.9 (16.5)	2.4 (9.5)	2.4 (10.8)	0.007 (−1.5 to 1.5)	.99
EQ-5D[b]								
Quotient score								
No. of patients	378	374	345	345	342	338	−0.03 (−0.07 to −0.002)	.04
Score	0.64 (0.27)	0.66 (0.25)	0.65 (0.25)	0.63 (0.26)	0.002 (0.23)	−0.03 (0.21)		
Visual analogue score								
No. of patients	376	376	346	347	341	342	−0.2 (−2.6 to 2.2)	.88
Score	68.5 (17.5)	68.6 (17.0)	67.4 (18.2)	66.8 (17.8)	−1.8 (17.1)	−1.9 (14.3)		

Abbreviations: EQ-5D, EuroQol-5D; NEADL, Nottingham Extended Activities of Daily Living; OT, occupational therapy; PDQ-39, Parkinson Disease Questionnaire-39; PT, physical therapy.

[a] To aid interpretation, regardless of scale, a positive mean difference favors no therapy group and a negative mean difference favors the PT/OT group.

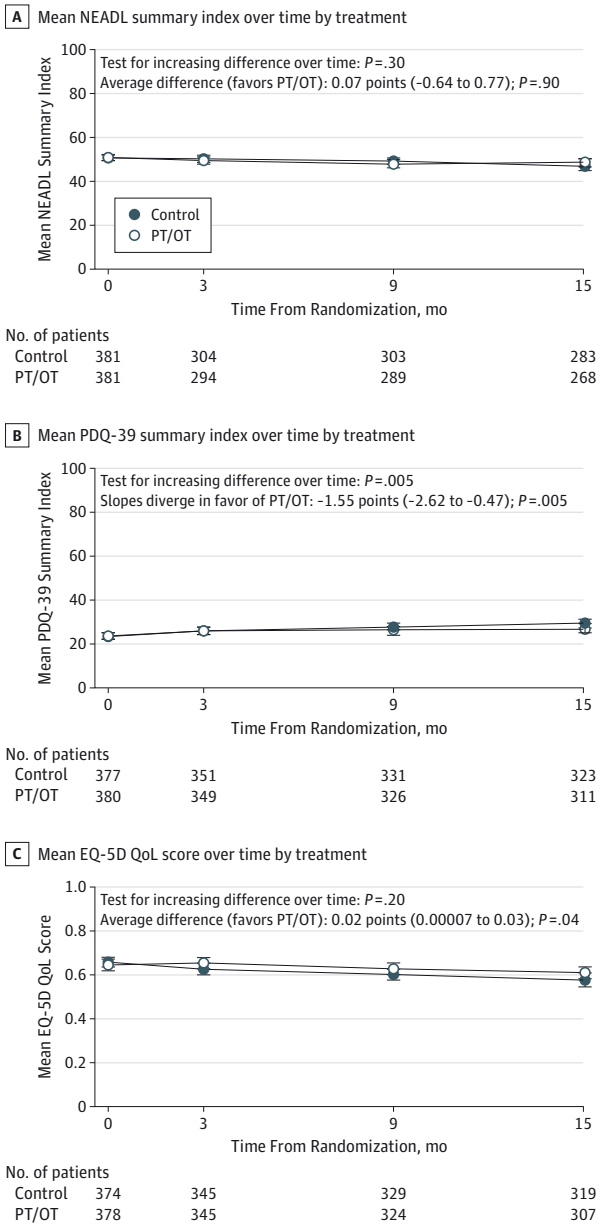
[b] The NEADL total score: ranges from 0 to 66, where higher scores are better and a positive change is an improvement in score. PDQ-39: ranges from 0 to 100, where lower scores are better and a negative change is an improvement in score. EQ-5D quotient: ranges from −0.59 to 1, where higher scores are better and a positive change is an improvement in score. EQ-5D VAS: ranges from 0 to 100, where higher scores are better and a positive change is an improvement in score.

minutes). Most PT was performed in outpatient settings (53%) rather than the community (39%) or other setting (8%), whereas OT was more commonly performed in the community (69%) rather than outpatient (29%) or other (2%) settings.

Physiotherapy logs showed the most frequent interventions were for gait (96% of patients; n = 330), posture (93%; n = 319), balance (90%; n = 310), physical conditioning (81%; n = 280), and transfers (79%; n = 271). Occupational therapy logs showed the most frequent interventions were for transfers (46%; n = 150), dressing and grooming (37%; n = 122), sleep and fatigue (32%; n = 105), indoor mobility (29%; n = 96), household tasks (29%; n = 95), and other environmental issues (28%; n = 93).

Validation of therapy logs was undertaken by comparing logs with full-text therapy notes for 38 patients chosen at random from 10 geographically diverse centers. Interventions were grouped into the following: assessment, equipment/adaptation prescription, exercise recommendations, referral to other specialists, and "other advice." Physiotherapists prescribed a range of exercise programs tailored to their assessment of patient mobility and activity levels. Only 3

Figure 2. Medium-term Scores in Activities of Daily Living and Quality of Life



EQ-5D indicates EuroQol-5D; NEADL, Nottingham Extended Activities of Daily Living; OT, occupational therapy; PDQ-39, Parkinson Disease Questionnaire-39; PT, physical therapy; QoL, quality of life.

physiotherapists provided specific PD exercise advice accompanied by a booklet, and there was no evidence of a formal exercise progression protocol for any patient. Occupational therapy assessed the full range of ADL, but predominant interventions were equipment provision, onward referral, and other advice (eg, management of sleep disorders and applying for benefits). There was little task-related practice.

Outcome Measures

The mean NEADL total score deteriorated from baseline to 3 months by 1.5 points in the therapies group compared with 1.0 point in the no therapy group (difference, 0.5 points; 95% CI, −0.7 to 1.7; P = .41; **Table 2**). No difference was seen in any of the individual categories of the NEADL score (Table 2). Repeated-measures analysis of the NEADL across all points showed no difference between the treatment arms (**Figure 2**; eTable 1 in Supplement 2).

The mean PDQ-39 summary index deteriorated by 2.4 points in both groups from baseline to 3 months (difference, 0.007 points; 95% CI, −1.5 to 1.5; P = .99; Table 2). No difference was seen in any of the 8 domains of the PDQ-39 (Table 2). The slight improvement of 0.002 points in the EQ-5D quotient in the therapies group between baseline and 3 months compared with a 0.03-point deterioration in the no therapy group was of borderline significance (difference, −0.03; 95% CI, −0.07 to −0.002; P = .04; Table 2). There was no difference in the EQ-5D visual analogue score (difference, −0.2; 95% CI, −2.6 to 2.2: P = .88; Table 2).

Repeated-measures analysis over 15 months found significant divergence in PDQ-39 summary index (curves diverging at 1.55 points per annum; 95% CI, 0.47-2.62; P = .005; Figure 2) and for the ADL, emotional well being, and social support domains in favor of therapy (eTable 2 in Supplement 2), but there was no difference in the mobility domain. There was also a borderline significant difference over time in the EQ-5D quotient in favor of the therapies arm (0.02; 95% CI, 0.00007-0.03; P = .04; Figure 2).

Sensitivity analysis with imputation of missing NEADL values did not change the results nor did repeating the PDQ-39 analysis without imputation of missing values using the expectation maximization algorithm affect the results. We also analyzed the primary outcome of mean change between baseline and 3 months for NEADL total score data using analysis of covariance, adjusting for baseline NEADL score and the other minimization variables, but this made no difference to the result.

Planned subgroup analyses for NEADL total score found no evidence of difference in therapy effect at 3 months according to baseline total NEADL score, age, or disease severity (eFigure in Supplement 2).

Four hundred and seventy three patients (62%) had a caregiver and 406 caregivers (86%) agreed to take part in the trial (mean age, 67 years; 76% female). The relationship between patient and caregiver was most often partner or spouse (72%). Although there was no difference in caregiver SF-12 physical component score at 3 months, there was less decline in caregiver SF-12 mental component score (difference, −2.1; 95 CI, −3.9 to -0.3; P = .02; **Table 3**) although this was not maintained with longer follow-up (eTable 3 and eTable 4 in Supplement 2).

Adverse Events

Targeted adverse events are detailed in eTable 5 in the Supplement 2. There were no differences in adverse events between trial arms at 3 or 15 months.

Discussion

The PD REHAB Trial showed that PT and OT were not associated with clinically meaningful immediate or medium-term beneficial effects on ADL or QoL in mild to moderate PD. The medium-

Table 3. Caregiver Quality of Life Scores

Scale	Mean (SD)						Mean Difference (95% CI)[a]	*P* Value
	Baseline		3 mo		Mean Change From Baseline			
	PT/OT	No Therapy	PT/OT	No Therapy	PT/OT	No Therapy		
SF-12[b]								
Physical functioning								
No. of patients	171	181	169	181	151	156	−5.6 (−11.0 to −0.2)	.04
Score	70.3 (35.4)	76.0 (30.5)	68.6 (35.8)	70.3 (30.0)	−0.7 (24.8)	−6.3 (23.0)		
Role physical								
No. of patients	173	183	169	185	155	163	−0.5 (−5.3 to 4.3)	.84
Score	75.4 (28.5)	76.7 (26.8)	69.8 (28.8)	71.0 (27.1)	−5.4 (19.6)	−5.9 (23.8)		
Role emotional								
No. of patients	172	182	170	183	155	162	−4.4 (−9.0 to 0.2)	.06
Score	83.6 (23.1)	81.9 (22.9)	80.4 (24.2)	76.4 (24.9)	−1.7 (20.0)	−6.1 (21.5)		
Social functioning								
No. of patients	175	186	171	189	157	169	−3.8 (−8.9 to 1.3)	.14
Score	84.9 (22.9)	83.3 (23.6)	81.0 (24.5)	78.3 (26.9)	−2.9 (21.9)	−6.7 (24.5)		
Mental health								
No. of patients	174	183	170	188	156	167	−4.3 (−8.2 to −0.4)	.03
Score	68.8 (21.1)	68.6 (18.5)	67.6 (20.2)	64.6 (21.9)	−0.2 (16.7)	−4.5 (18.9)		
Vitality								
No. of patients	175	184	170	188	156	167	−4.6 (−9.2 to 0.05)	.05
Score	57.4 (25.6)	61.8 (22.6)	53.8 (25.9)	53.2 (24.5)	−3.5 (21.0)	−8.1 (21.1)		
Bodily pain								
No. of patients	173	184	170	189	156	168	2.9 (−2.2 to 7.9)	.27
Score	77.7 (29.3)	76.4 (28.7)	74.1 (28.8)	74.2 (28.5)	−4.6 (25.0)	−1.8 (21.1)		
General health								
No. of patients	174	186	170	190	155	170	−0.9 (−5.0 to 3.3)	.68
Score	64.2 (25.3)	65.6 (26.1)	58.9 (26.0)	61.0 (25.3)	−4.4 (18.6)	−5.3 (19.5)		
Component score								
Physical								
No. of patients	166	171	165	174	146	144	−0.6 (−2.3 to 1.2)	.53
Score	47.1 (12.5)	48.2 (11.4)	45.1 (13.3)	46.4 (11.6)	−1.6 (7.5)	−2.1 (7.5)		
Mental								
No. of patients	166	171	165	174	146	144	−2.1 (−3.9 to −0.3)	.02
Score	51.1 (10.2)	50.1 (8.9)	49.7 (10.2)	48.0 (10.5)	−0.5 (7.6)	−2.6 (7.9)		

Abbreviations: OT, occupational therapy; PT, physical therapy; SF-12, Short Form–12.

[a] To aid interpretation, regardless of scale, a positive mean difference favors no therapy group and a negative mean difference favors PT/OT group.

[b] SF-12: ranges from 0 to 100 where higher scores are better and a positive change is an improvement in score.

term significant differences in QoL measured by PDQ-39 summary index and EQ-5D quotient in favor of therapy were small and did not reach clinically significant levels, which we defined as twice the minimally clinically important change levels.

Our Cochrane review of PT vs no intervention in PD showed that all forms of PT produced small benefits in motor function and ADL but no change in QoL.[19] The Cochrane review of OT found insufficient evidence about effectiveness in 2 small trials,[4] although a large (n = 191) Dutch trial found that OT improved self-perceived performance but not QoL.[20] The absence of any motor effect (PDQ-39 mobility domain) or response in ADL in the PD REHAB Trial is likely to be multifactorial owing to early disease stage of most patients, low "dose" of intervention, and lack of consistency in therapy assessment and intervention.

Traditionally, PT and OT have been used in the more advanced stages of PD, once imbalance and falls have developed (H&Y stage ≥3).[1] As a result of using the uncertainty principle for entry into the trial, most patients in the PD REHAB Trial had H&Y stage less than 3 at randomization. It is possible that such mild to moderate disease may not respond to the therapies, whereas more severe disease may respond, although this remains to be established. As a consequence, the results of the PD REHAB Trial can only be generalized to patients with mild to moderate disease.

Median therapy dose was 4 sessions of 58 minutes over 8 weeks for both therapies combined. This is low in comparison with the 5 PT trials in the Cochrane review (5-52 weeks of therapy).[3] In a Dutch trial of PT in PD (ParkinsonNet),[21] total contact time (over 6 months) between patients and physiotherapists was 15 sessions of 30 minutes, nearly double that in the PD REHAB Trial, but the study also showed no evidence in favor of therapy. Importantly, the dose delivered in the PD REHAB Trial reflects routine NHS practice.

Therapy expert groups recommended an individual "goal-setting" approach for PD REHAB interventions because this is the gold standard and addresses the personalized needs and wishes of the individual. Therapy content was in keeping with NHS and European guidelines on PT and OT.[8-11] However, an individualized goal-setting approach with this content may not be transferable to patients with mild disease. The lack of task-related practice is of particular concern because this has been shown to be a significant factor in stroke rehabilitation trials.[22] We were also concerned by the low prescription and dose of exercise in the PD REHAB Trial.

The possibility that patients with more severe disease might show a better response was examined in a planned subgroup analysis examining response according to baseline NEADL score and H&Y stage. While the data did not support this hypothesis, the numbers with severe disease were small, so this is likely to be underpowered. Similarly, older patients might respond better to the therapies because of greater levels of frailty and comorbidities, but there was no evidence of this in the subgroup analysis.

The fidelity of the intervention was reasonable in both arms of this pragmatic real-world trial. In the therapies arm, 93% of patients (n = 353) received therapies within 3 months of randomization. Whereas, only 2% (n = 9) of the no therapy arm crossed over to receive treatment within 3 months, mainly owing to motor progression. It is unlikely that these small proportions of crossovers led to the lack of effect seen in the trial.

Despite all patients reporting ADL problems at baseline, many had mild disease. A total of 29% (n = 221) had a NEADL score at baseline of greater than 61 and 14% (n = 107) had a score of 65 or greater (mean baseline score, 51). This may have led to a floor effect because the NEADL score could not improve much from a good baseline score. However, planned subgroup analysis showed that there was still no response in patients with more severe baseline NEADL scores. It should also be noted that the NEADL results are supported by the lack of a clinically meaningful effect on PDQ-39 ADL domain.

Conclusions

Physiotherapy and OT using an individual goal-setting approach produced no clinically meaningful short- or medium-term benefits in ADL or QoL in patients with mild to moderate PD. This evidence does not support the use of low-dose, goal-directed PT and OT in patients in the early stages of PD. Future research should explore the development and testing of more structured and intensive PT programs in patients with all stages of PD.

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Author Affiliations: School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, England (Clarke); Department of Neurology, Sandwell and West Birmingham Hospitals NHS Trust, City Hospital, Birmingham, England (Clarke); Birmingham Clinical Trials Unit, College of Medical and Dental Sciences, University of Birmingham, Birmingham, England (Patel, Ives, Rick, Dowling, Woolley); Cancer Research UK Clinical Trials Unit, College of Medical and Dental Sciences, University of Birmingham, Birmingham, England (Wheatley); University of Nottingham, Nottingham, England (Walker); King's College, London, England (Sackley).

Author Contributions: Dr Clarke had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Clarke, Ives, Wheatley, Walker, Sackley.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Clarke, Patel, Ives, Wheatley, Walker, Sackley.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Patel, Ives, Woolley, Wheatley.
Obtained funding: Clarke, Ives, Wheatley, Walker, Sackley.
Administrative, technical, or material support: Clarke, Rick, Dowling, Walker.
Study supervision: Clarke, Ives, Wheatley, Walker, Sackley.

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Group Information: The PD REHAB Collaborative Group members include the following: Trial Management Center: *University of Birmingham Clinical Trials Unit*: P. Au, V. Cheed, F. Dowling, N. Hilken, N. Ives, C. Meek, R. Ottridge, S. Patel, C. Rick, E. Tyler, K. Wheatley, A. Wilcockson, and R. Woolley. *University of Birmingham, Birmingham:* C. E. Clarke (chief investigator, neurologist). *King's College, London:* C. M. Sackley (physiotherapy lead). *University of Nottingham, Nottingham:* M. F. Walker (occupational therapy lead). *University of Southampton, Southampton:* G. Yao (health economics). Trial Steering Committee: D. Burn (chair), K. Breen, H. Bridge, C. E. Clarke, H. Dawes, D. MacMahon, T. Malone, P. Ohri, H. Roberts, C. Sackley, and L. Wolstenholme. Data Monitoring and Ethics Committee: G. Kwakkel (chair), N. Bajaj, J. Gladman, and L. Hiller. Therapy Expert Groups: A. Aragon, A. Birleson, P. Chapman, V. Goodwin, A. Keene, V. Kelly, F. Lindop, E. Morgan, B. Ramaswamy, and L. Rochester. Service Users Group: H. Bridge, R. Coelho, K. Gordon, S. Herron-Marx, J. Morgan, D. Muir Wood, R. Norton, R. Patel, A. Peet, C. Sanders, S. Shah, J. Taylor, G. Thorpe, E. W. K. Young.

Participating Centers and PD REHAB Collaborative Group Members: *Aberdeen Royal Infirmary, Aberdeen:* S. Armour, C. Counsell (principal investigator [PI] at site), C. Harris, C. Knight, V. Leslie, and M. Ord. *Central Middlesex Hospital, London:* R. Bharmal, N. Idris, A. Lacey, S. Molloy [PI], C. Mummery, M. Patel, C. Sequeira, G. Sharma, and E. White. *City Hospital, Birmingham:* A. Billingham, K. Blachford, C. E. Clarke [PI], C. Coley, T. Doxsey, C. Holdsworth, C. Kanakaratna, F. Kinney, D. Nicholl, S. Purkis, F. Siddiqui, and C. Street. *Cumberland Infirmary, Carlisle:* B. Bishop, J. Bowyer, J. George [PI], A. Hampson, and V. Marshall. *Darlington Memorial Hospital, Darlington:* L. Alderton, S. Ayirookuzhi, S. Carney, P. Carr, L. Cochrane, M. Corr, L. Curran, C. Deacon, S. Hilton, A. Martin, M. Omole, R. Prescott [PI], A. Rose, and H. Watson. *Dorset County Hospital, Dorchester:* M. Baker, S. Breakspear, B. Burgess, S. Caddy, S. Carr, S. Chaplin, C. Coleman, R. Gregory [PI], A. Jones, L. O'Shea, H. Read, S. Richardson, and L. Villanueva. *Eryri Hospital, Caernarfon:* J. Hindle, P. Ohri [PI], A. Owen, C. Pritchard, E. Roberts, and Ff. Williams. *Fairfield General Hospital, Bury:* A. Ansari, K. Birtwell, J. Brooke, L. Craven, A. Drogan, E. Hill, E. Johnson, E. Oughton, J. Raw [PI], C. Thistlewaite, and T. Wijethunge. *Gloucestershire Royal Hospital, Gloucester:* K. Bird, P. Brown, F. Clayton-Smith, F. Davis, H. Dix, P. Fletcher [PI], E. Folkes, V. Hardwick, K. Harrison, K. Keene, P. Medcalf, P. Morrish, M. Silva, G. Thistlewood, and H. Wilson.

Lincolnshire Hospitals, Lincoln and Grantham: D. Boyer, L. Crisp, A. Kirjazovas, H. Lister, A. Macedonska, E. Munyonga, R. Norton, C. Rees, B. Sharrack, J. Sharma [PI], K. Shelbourn, S. Strickland, and E. Ward. *Harrogate District Hospital, Harrogate:* P. Bagot, G. Burton, A. Gillespie, E. Jackson, S. Smith, G. Wihl [PI], and R. Worton. *Hereford County Hospital, Hereford:* M. Cottrell, J. Dalziel, C. Evans, D. Kent, P. Matheson, and E. Wales [PI]. *Hull Royal Infirmary, Hull:* J. Cook, J. Curran, A. Ming [PI], and D. Parker. *Leicester General Hospital, Leicester:* D. Bovington, C. Brownson, K. Castle, N. Clague, S. Forrest, N. Lavin, J. Lindsay, N. Lo [PI], J. Lokat, R. MacDonald, K. MacSwiney, S. Seaman, and J. Taylor. *Macclesfield District General Hospital, Macclesfield:* K. Bullivant, A. Crosby, R. Graba, E. Oughton, S. Raybould, D. Rowarth, H. Rooney, M. Silverdale [PI], C. Vandor, H. Vanek, and T. Wright. *Mount Gould Hospital, Plymouth:* H. Brookes, S. Edwards, B. Dingle, M. Holme, K. Jones, G. Kendall, S. Mahadik [PI], F. Murphy, K. Stocker, M.-J. Trimmer, and M. Visick. *Musgrove Park Hospital, Taunton:* R. Chorley, S. Cooper [PI], A. Dawton, C. Henley, J. Homan, D. Sharratt, and J. Vassalli. *Newmarket Community Hospital, Newmarket:* G. Calderon, L. Canovas, M. Glass, S. Hooley, W. Houghton, A. Jackson, G. Lennox [PI], A. South, and T. Ward. *Norfolk and Norwich University Hospital, Norwich :* A. Clark, P. Crosby, C. Herrington, A. Hursey, C. Garrett, K. Goddard, L. Reynolds, J. Taylor, J. West, and P. Worth [PI]. *North Devon District Hospital, Barnstaple:* G. Harper [PI], S. Hilsdon, T. Harrower, S. Pike, and N. Vernon. *Peterborough City Hospital, Peterborough:* G. Calderon, L. Canovas, E. Davies, C. Farrar, S. Guptha [PI], A. Jackson, C. Noble, and J. Sheldrake. *Poole General Hospital, Poole:* L. Chohra, C. Cooper, M. Goddard, R. Gregory [PI], G. King, and V. Stone. *Princess of Wales Hospital, Bridgend:* L. Ebenezer, R. Gdesis, C. Muller, S. Raha [PI], P. Sloan, S. Thomson, and R. Turner. *Queen Alexandra Hospital, Portsmouth:* M. Chawner, C. Delves, C. Edwards, C. Francis, W. Gibb, Z. Hemsley [PI], J. Hewitt, E. Hoysted, K. Lapicki, T. Jepp, S. Marsh, A. McBride, E. McNaughton, S. Pearce, C. Rayner, C. Saunders, A. Stephenson, B. Uwe, J. Walker, and L. Wimshurst. *Royal Blackburn Hospital, Blackburn:* J. Birt, S. Crane, M. Hare, C. Kenyon, L. McToal, P. Tidswell [PI], N. Verstraelen, and K. Ward. *Royal Bournemouth General Hospital, Bournemouth:* K. Amar [PI], S. Atkins, C. Cooper, L. du Preez, G. Hodges, G. King, K. Kuhr, T. Senyard, C. Thompson, and B. Utting. *Royal Devon & Exeter Hospital, Exeter:* C. Askham, B. Bailey, W. Blour, L. Butler, F. Chanton, C. Davies, R. Elliott, G. Fenwick, D. Gladman, K. Gormley, F. Havlin, T. Harrower, J. Holman, S. Irvine, R. James, A.-M. Jones, D. Kendrick, R. Lane, T. Malone [PI], V. Matthews, T. Morris, L. Morley, V. Pearce, A. Potter, K. Priestner, A. Quthue-Jones, F. Robotham, R. Sheridan, C. Smith, K. Smith, A. Souster, V. Wilkins, and A. Woodger. *Royal Hampshire County Hospital, Winchester:* C. Barlow, E. Carroll, E. Ghazaros, C. Gordon [PI], T. McElwaine, and H. Slater. *Royal Preston Hospital, Preston:* J. Bimson, J. Birt, S. Cornall, M. Hare, T. Majeed [PI], J. Pearson, D. Stephenson, R. Turner, N. Verstraelen, and K. Ward. *St Helens and Knowsley Hospitals, St Helen:* J. Abrams [PI], C. Andrew, S. Ashley, D. Dufay, D. Gandecha, A. Howman, L. Molloy, E. Oughton, H. Rayner, and N. Smith. *Salisbury District Hospital, Salisbury:* K. Grainger, J. Lee, and J. Marigold [PI]. *Southampton General Hospital, Southampton:* V. Agarwal, L. Ashdown, C. Carden-Noad, C. Dean, C. Edwards, G. Howard, and H. Roberts [PI]. *Torbay District General Hospital, Torbay:* L. Halfhide, A. Hall, G. Kendall [PI], P. McConkey, P. Mercer, and K. Roberts. *Walton Center for Neurology & Neurosurgery, Liverpool:* S. Burns, D. Davies, A. Deaves, N. Hallissey, L. Hughes, H. McGuinn, A. P. Moore [PI], I. O'Brien, H. O'Heary, N. Porter, M. Steiger, D. Watling, L. Webb, and L. Wyatt. *Weston General Hospital, Weston-super-Mare:* S. Barber, S. Bedford, H. Dymond, P. Easton, F. Henchie, K. Powell, R. Roberts [PI], G. Saunders, D. Simmons, and S. Whitford. *William Harvey Hospital, Ashford:* J. Hawkins, A. Heller, L. Hills, M. Jenkinson, M. McHenry, N. Munro, M. Sakel, M. Samuel [PI], N. Scoble, K. Turner, R. Vahid, and A. Vincent. *Yeovil District Hospital, Yeovil:* K. Baker, H. Brunt, C. Buckley, M. Jones, K. Randall, C. Redman, R. Rowland-Axe, R. Sophia [PI], and R. Tonkin.

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REFERENCES

1. National Collaborating Centre for Chronic Conditions. *National Institute for Health and Clinical Excellence (NICE) Guidelines: Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care*. London, England: Royal College of Physicians; 2006.

2. Tomlinson CL, Herd CP, Clarke CE, et al. Physiotherapy for Parkinson's disease: a comparison of techniques. *Cochrane Database Syst Rev*. 2014;6:CD002815.

3. Tomlinson CL, Patel S, Meek C, et al. Physiotherapy versus placebo or no intervention in Parkinson's disease. *Cochrane Database Syst Rev*. 2013;9:CD002817.

4. Dixon L, Duncan D, Johnson P, et al. Occupational therapy for patients with Parkinson's disease. *Cochrane Database Syst Rev*. 2007;(3):CD002813.

5. Clarke CE, Furmston A, Morgan E, et al. Pilot randomised controlled trial of occupational therapy to optimise independence in Parkinson's disease: the PD OT trial. *J Neurol Neurosurg Psychiatry*. 2009;80(9):976-978.

6. Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1988;51(6):745-752.

7. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. 1967;17(5):427-442.

8. Plant RP, Jones D, Ashburn A, et al. *Evaluation of Physiotherapy in Parkinson's Disease: Project Update: The Science and Practice of Multidisciplinary Care in Parkinson's Disease and Parkinsonism*. London, England: British Geriatric Society; 1999.

9. Keus S, Hendriks H, Bloem B, et al. KNGF clinical practice guideline for physical therapy in patients with Parkinson's disease. *Dutch J Physiotherapy*. 2004;114(3).

10. Deane K, Ellis-Hill C, Dekker K, Davies P, Clarke CE. A survey of current occupational therapy practice for Parkinson's disease in the United Kingdom. *Br J Occup Ther*. 2003;66:193-200.

11. Deane K, Ellis-Hill C, Dekker K, Davies P, Clarke CE. A Delphi survey of best practice occupational therapy practice for Parkinson's disease in the United Kingdom. *Br J Occup Ther*. 2003;66:247-254.

12. Ebrahim S, Nouri F, Barer D. Measuring disability after a stroke. *J Epidemiol Community Health*. 1985;39(1):86-89.

13. Legg L, Drummond A, Leonardi-Bee J, et al. Occupational therapy for patients with problems in personal activities of daily living after stroke: systematic review of randomised trials. *BMJ*. 2007;335(7626):922.

14. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing*. 1997;26(5):353-357.

15. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord*. 2010;25(15):2649-2653.

16. Walker MF, Gladman JR, Lincoln NB, Siemonsma P, Whiteley T. Occupational therapy for stroke patients not admitted to hospital: a randomised controlled trial. *Lancet*. 1999;354(9175):278-280.

17. Schafer J. *Analysis of Incomplete Multivariate Data*. London, England: Chapman & Hall; 1999.

18. Jenkinson C, Heffernan C, Doll H, Fitzpatrick R. The Parkinson's Disease Questionnaire (PDQ-39): evidence for a method of imputing missing data. *Age Ageing*. 2006;35(5):497-502.

19. Tomlinson CL, Patel S, Meek C, et al. Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis. *BMJ*. 2012;345:e5004.

20. Sturkenboom IH, Graff MJ, Hendriks JC, et al; OTiP study group. Efficacy of occupational therapy for patients with Parkinson's disease: a randomised controlled trial. *Lancet Neurol*. 2014;13(6):557-566.

21. Munneke M, Nijkrake MJ, Keus SH, et al; ParkinsonNet Trial Study Group. Efficacy of community-based physiotherapy networks for patients with Parkinson's disease: a cluster-randomised trial. *Lancet Neurol*. 2010;9(1):46-54.

22. Walker MF. Stroke rehabilitation: evidence-based or evidence-tinged? *J Rehabil Med*. 2007;39(3):193-197.