Effect of Exercise on Motor Symptoms in Patients With Parkinson's Disease: A Network Meta-analysis

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ABSTRACT

Background: Although the pharmacological approach may help with motor symptoms in Parkinson's disease (PD), they are clearly not the complete solution. Thus, for the treatment of PD motor symptoms, physical activity has been proposed as an effective intervention.

Methods: A systematic search in MEDLINE, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials databases was conducted to identify randomized controlled trials testing the effectiveness of exercise interventions on motor symptoms of PD. Physical exercise interventions were divided into 9 categories: endurance, resistance, combined, balance, dance, alternative exercises, body weight supported, sensorimotor interventions including endurance exercise, and sensorimotor interventions not including endurance exercise. A pairwise meta-analysis for direct and indirect comparisons between intervention and control/nonintervention groups was carried out.

Results: Fifty-six studies met the inclusion criteria, including 2740 participants, aged between 57.6 and 77.7 years. Results showed that sensorimotor training including endurance (effect size [ES]−1.09; 95% confidence interval [CI], −1.68 to −0.50), resistance (ES−0.82; 95% CI, −1.23 to −0.41), and dance (ES−0.64; 95% CI, −1.24 to −0.05) were the most effective physical activity interventions for mitigating PD motor symptoms.

Conclusion: Physical activity interventions are an effective strategy for the management of motor symptoms in patients with PD. Among the different exercise intervention programs, those including more complex and demanding activities (sensorimotor training including endurance, resistance, and dance) seem to be the most effective physical activity interventions.

Key Words: ageing, effectiveness, exercise rehabilitation

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CLINICAL HIGHLIGHTS

- So far, there is no substantial evidence showing the most effective exercise program for Parkinson's disease (PD) motor symptoms.
- Physical activity interventions are effective in the management of PD motor symptoms, with sensorimotor training including endurance being the most effective one.
- This information is of use to clinicians prescribing exercise for mitigating patients' motor symptoms and promoting their independence in activities of daily living.

INTRODUCTION

Parkinson's disease (PD) is a common, chronic, and progressive neurological disorder with a universal age-adjusted

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incidence rate ranging from 9.7 to 13.8 per 100 000 cases per year.[1] It is characterized by the predominant presence of motor symptoms, such as bradykinesia, rigidity, tremor, and postural instability, which are frequently associated with nonmotor symptoms.[1]

The diagnosis of PD implies a progressive motor impairment and disability affecting patients' everyday activities and quality of life.[2] Pharmacological and surgical treatments may help in the management of PD symptoms, but they do not completely address motor symptoms of PD as it is an incurable and progressive neurodegenerative disease.[3] Furthermore, regular leisure-time physical activity and exercise program engagement can reduce the risk of developing PD because of their neuroprotective effect through upregulation of brain-derived nerve growth factors.[4]

Apart from their preventive effect, rehabilitation protocols that include exercise interventions adapted to patients with PD are considered a new approach to cope with the remaining motor disabilities.[5,6] The common aim of these physical activity programs is to deal with long-lasting motor symptoms through the preservation and improvement of motor functions, thereby improving global health. Several types of exercise have been included in these PD-adapted programs, such as body weight support exercises, adapted dance, tai chi, yoga, endurance, and strength physical activity programs.[7-9] Specific PD-adapted programs have shown benefits in physical functioning, health-related quality of life, strength, and balance and gait speed, although there is insufficient evidence on their efficacy on reducing falls or depression in people with PD.[7-12] Although so far, there is no consistent evidence on which type of exercise shows the greater effects for reducing PD motor symptoms.

Frequently, PD symptoms have been measured using the Unified Parkinson's Disease Rating Scale (UPDRS),[13] which ensure fair comparisons among studies and include a specific section for PD motor symptoms that consist of a combination of the following motor symptoms: speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity on movement, postural tremor of the hands, rest tremor amplitude, and constancy of the rest tremor.

Therefore, the aim of this systematic review and meta-analysis was to provide evidence regarding the effectiveness of exercise programs on relieving motor symptoms of PD measured using the motor part of the UPDRS scale by comparing different types of exercise programs.

METHODS

This network meta-analysis was guided by the Cochrane Collaboration Handbook[14] and reported following the PRISMA statement extension for systematic reviews incorporating network meta-analysis (PRISMA-NMA) statement.[15] The protocol for this network meta-analysis has been registered on PROSPERO (CRD42018087765).

Data Sources and Searches

We searched MEDLINE (via PubMed), Web of Science, Scopus, and Cochrane Central Register of Controlled Trials from their inception to April 2021, aiming to identify studies on the effect of physical exercise interventions on motor symptoms of patients with PD, measured by the motor part of UPDRS. This scale is the most widely used clinical rating scale for PD.[13]

The search strategy included the following terms: "Parkinson," "Parkinson Disease," "physical exercise," "exercise," "CRF," "$\dot{V}o_{2max}$," "fitness," "cardiorespiratory fitness," "aerobic fitness," "physical fitness," "muscular resistance," "physical endurance," "muscular endurance," and "muscular strength." In addition, previous systematic reviews and meta-analyses in the issue and reference lists of the included studies were reviewed for any relevant study. The complete strategy search for MEDLINE is available in Supplemental Digital Content Table 1, available at: http://links.lww.com/JGPT/A75.

The Study Selection

This network meta-analysis includes studies on the effect of physical exercise interventions on the motor symptoms of patients with PD. Inclusion criteria were as follows: (i) participants: adults; (ii) exposure: physical exercise programs; (iii) outcome: motor symptoms of PD measured using the motor part of the UPDRS; and (iv) study design: randomized and nonrandomized controlled trials. No language restrictions were applied.

Studies were excluded when (i) they focused on children or adolescents, (ii) PD motor symptoms were rated using scales other than UPDRS, (iii) they did not include a control group and included different intervention groups developing similar exercise programs, or (iv) they were designed as crossover studies and did not report results at the end of the first intervention period.

Data Extraction and Risk of Bias

We summarized the main characteristics of the included studies in Table 1, including the following: (1) characteristics of participants (sample size, including number of females, mean age, duration of PD, type of population, and basal Hoehn and Yahr stage (H&Y) and UPDRS scores), and (2) physical exercise intervention characteristics (intervention description and dose [length of the intervention, sessions per week, and duration of sessions]).

The included studies were assessed using the Cochrane Collaboration tool for assessing risk of bias (RoB2).[16] This tool assesses the risk of bias according to 6 domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias due to measurement of the outcome, bias due to selection of the reported result, and overall bias. The overall bias of each study was considered as "low risk of bias" when the study was classified as "low risk" in all domains, "some concerns" when there was at least 1 domain classified as "some concern," and

Table 1. Characteristics of the Included Studies[a]

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Abraham et al[24] (2018)	United States	IG: 10 (1) CG: 10 (3)	IG: 66.4 (12.5) CG: 65.1 (7.5)	IG: 6.1 (3.8) CG: 8.5 (4.5)	IG: 2.0 (1.8-2.5)[b] CG: 2.0 (2.0-2.5)[b]	IG: 38.4 (13.8) CG: 32.1 (12.2)	IG: Dynamic neurocognitive imagery (DNI) CG: health education	IG: 15-min warm-up + 45-min DNI concept introduction and practice part A and B + 20-min DNI movement session + 5-min DNI cool-down/wrap-up CG: 90-min read 1 lesson + 30-min exercises on video	2 w-5 sxw (120 min)
Acarer et al[25] (2015)	Turkey	IG: 29 (12) CG: 11 (3)	IG: 67 (51-81) CG: 60 (40-71)	IG: 4.5 (1-24) CG: 8 (1-18)	IG: 22 in stage II CG: 6 in stage II	IG: 19.5 (10-54)[b] CG: 25 (8-41)[b]	IG: customized vestibular rehabilitation CG: control group	IG: adaptation exercises + substitution exercise + habituation exercises + balance exercises + home-based exercises CG: usual care	8 w-1 sxw (30-45 min) + 2 sxd of home-based exercise (30-40 min)
Almeida and Bhatt[26] (2012)	Canada	IG1. 14 (6) IG2: 14 (2) CG: 14 (3)	IG1: 63.86 (8.41) IG2: 73.93 (6.53) CG: 67.43 (9.26)	NA	NA	IG1: 23.68 (10.1) IG2: 22.07 (8.0) CG: 24.21 (9.5)	IG1: treadmill group IG2: overground group CG: control group	IG1: treadmill gaiting on equally distributed spaced cues IG2: overground gait on equal spaced cues on carpet	6 w-3 sxw (30 min)
Amano et al[27] (2013)	United States	IG1: 12 (5) IG2: 15 (8) IG3: 9 (2) CG: 9 (2)	IG1: 64 (13) IG2: 66 (11) IG3: 68 (7) CG: 66 (7)	IG1: 7 (7) IG2: 8 (5) IG3: 12 (7) CG: 5 (3)	IG1: 2.3 (0.4) IG2: 2.4 (0.6) IG3: 2.2 (0.4) CG: 2.4 (0.4)	IG1: 21.1 (6.8) IG2: 23.1 (6.0) IG3: 24.1 (5.7) CG: 23.1 (4.8)	IG1 and IG2: tai chi exercise IG3: Qi-Gong meditation CG: usual care	IG1 and IG2: Yang-style short forms IG3: Qi-Gong meditation	IG1:16 w-2 sxw (60 min) IG2:16 w-3 sxw (60 min) IG3:16 w-2 sxw (60 min)
Ayán and Cancela[28] (2012)	Spain	IG1: 10 (6) IG2: 10 (5)	IG1: 68.9 (9.6) IG2: 71.9 (5.1)	IG1: 6.1 (3.1) IG2: 7.5 (5.5)	IG1: 2.4 (0.7) IG2: 2.0 (0.7)	IG1: 13.7 (6.9) IG2: 16.2 (6.6)	IG1: low-intensity water-based exercise IG2: muscular resistance water-based exercise	IG1: 10-min warm-up + 20-min balance exercises + 15-min dynamic exercises + 10-min cool-down IG2: 15-min warm-up + 30-min muscular resistance + 15-min cool-down	12 w-2 sxw (60 min)

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Beck et al[29] (2018)	Canada	IG1: 19 (4) IG2: 20 (4) CG: 11 (1)	IG1: 68.63 (9.91) IG2: 73.05 (7.84) CG: 71.27 (6.57)	IG1: 7.0 (5.01) IG2: 6.70 (4.16) CG: 8.36 (5.87)	NA	IG1: 20.08 (11.41) IG2: 22.89 (8.15) CG: 16.91 (9.20)	IG1: external focus of attention exercise IG2: internal focus on attention exercise CG: usual care	IG1: walking, balance, stretching, and coordination exercises with attention focused on movement of labels IG2: walking, balance, stretching, and coordination exercises with attention focused exercise on movement of limbs	11 w-3 sxw (60 min)
Burini et al[30] (2006)	Italy	IG1: 13 (8) IG2: 13 (9)	IG1: 65.7 (7) IG2: 62.7 (4)	IG1: 11.2 (5.4) IG2: 10.6 (4.8)	IG1: 3 in stage II IG2: 4 in stage II	IG1: 11 (2-16)[b] IG2: 12 (5-20)[b]	IG1: aerobic training IG2: Gi-gong group	IG1:10-min warm-up + 30-min cycle ergometer at 50%-60% HR + 10-min cool-down IG2: Gi-gong as Chinese physiotherapy approach	IG1: 7 w-3 sxw (45 min) IG2: 7 w-3 sxw (50 min)
Canning et al[31] (2012)	Australia	IG:10 (5) CG: 10 (4)	IG: 60.7 (5.9) CG: 62.9 (9.9)	IG: 6.1 (4.0) CG: 5.2 (4.1)	NA	IG: 20.9 (10.2) CG: 17.9 (7.1)	IG: semi-supervised home-based exercise program of treadmill walking CG: usual care	IG: warm-up + treadmill walking at 60%-80% of average speed + cold-down	6 w-4 sxw (30-40 min)
Carda et al[32] (2012)	Italy	IG1: 15 (NA) IG2: 15 (NA)	IG1: 67.87 (7.05) IG2: 66.93 (5.13)	IG1: 3.73 (2.49) IG2: 3.73 (1.91)	IG1: 2.17 (0.24) IG2: 2.23 (0.26)	IG1: 10.33 (8.89-11.78) IG2: 10.73 (9.32-12.14)	IG1: robot treadmill walking IG2: treadmill walking	IG1: 15 min at 50% BWS + 15 min at 30% BWS, at 1.5-3.0 km/h IG2: 30-min treadmill at 80%-100% maximum speed	4 w-3 sxw (30 min)
Carrol et al[33] (2017)	Ireland	IG: 10 (3) CG: 8 (3)	IG: 69.5 (57.75-71.75)[b] CG: 74 (67-77)[b]	IG: 7 (3.25-12.25)[b] CG: 10.5 (4.25-13.5)[b]	IG: 2.0 (1.5-2.25)[b] CG: 2.0 (1.63-2.88)[b]	IG: 17.5 (8.75-21.25)[b] CG: 16.5 (10.25-21.25)[b]	IG: aquatic gait training CG: usual care	IG: 10-min warm-up + 25-min gait training + 10-min cool-down	6 w-2 sxw (45 min)
Cheng et al[34] (2017)	Taiwan	IG: 12 (3) CG: 12 (4)	IG: 65.8 (11.5) CG: 67.3 (6.4)	IG: 6.1 (4.1) CG: 8.1 (4.6)	IG: 1.8 (0.6) CG: 2.0 (0.8)	IG: 19.7 (4.2) CG: 19.5 (6.3)	IG: curved treadmill walking CG: trunk exercise	IG: 15-min turning-based treadmill each direction starting on 80% of comfortable speed + 10-min walking on ground CG: 30-min trunk-arm exercises in a sitting position + 10-min walking on ground	4-6 w-12 s (40 min)

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Cheon et al[35] (2013)	Korea	IG1: 7 (7) IG2: 9 (9) CG: 7 (7)	IG1: 62.3 (6.5) IG2: 65.6 (7.9) CG: 64.9 (7.2)	IG1: 5.8 (3.4) IG2: 6.1 (2.9) CG: 4.7 (4.2)	IG1: 2.5 (2-3)[b] IG2: 2.5 (2-3)[b] CG: 2.5 (2-3)[b]	IG1: 33.9 (15.3) IG2: 19.8 (9.0) CG: 32.8 (6.2)	IG1: combined exercise program IG2: tai chi exercise CG: no intervention	IG1: 5- to 10-min warm-up + 40- to 50-min combined exercise + 5-min cool-down IG2: 5- to 10-min warm-up + 40- to 50-min Sun style tai chi + 5-min cool-down	8 w-3 sxw
Choi et al[36] (2013)	Korea	IG:11 (NA) CG: 9 (NA)	IG: 60.81 (7.6) CG: 65.54 (6.8)	IG: 5.2 (2.7) CG: 5.2 (2.7)	IG: 1.6 (0.6) CG: 1.8 (0.3)	IG: 22.36 (7.44) CG:17.67 (8.21)	IG: tai chi intervention CG: no-exercise intervention	IG: 10-min warm-up + 30-min tai chi exercises + 10-min meditation + 10-min cool-down	12 w-2 sxw (50 min) +1 sxw home-based exercise
Collet et al[37] (2017)	United Kingdom	IG: 54 (23) CG: 51 (21)	IG: 66 (9) CG: 67 (7)	IG: 4.8 (4.1) CG: 5.3 (4.1)	NA	IG: 16.7 (10.1) CG: 19.9 (9.9)	IG: aerobic exercise CG: handwriting	IG: 30 min of aerobic training at 55%-85% HR + 30-min resistance training CG: "warm-up" hand exercises + writing exercises + hand exercises	24 w-2 sxw (60 min)
Corcos et al[38] (2013) (a los 6 m)	United States	IG1: 24 (10) IG2: 24 (10)	IG1: 58.6 (5.6) IG2: 59.0 (4.6)	IG1: 6.5 (4.7) IG2: 6.5 (4.1)	IG1: 2.3 (0.53) IG2: 2.2 (0.41)	IG1: 20.9 (8.0) IG2: 21.6 (10.1)	IG1: modified fitness counts IG2: progressive resistance training	IG1: stretches + balance + breathing + nonprogressive strengthening IG2: strengthening exercises	24 w-2 sxw (60-90 min)
Cugusi et al[39] (2015)	Italy	IG: 10 (2) CG: 10 (2)	IG: 68.1 (8.7) CG: 66.6 (7.3)	IG: 7 (2) CG: 7 (4)	IG: 2.4 (0.8) CG: 2.3 (0.5)	IG: 25.3 (11.1) CG: 25.0 (11.8)	IG: Nordic walking program CG: usual care	IG: warm up + practicing Nordic walking at 60%-80% of HRR + cool-down	12 w-2 sxw (60 min)
Dipascuale et al[40] (2017)	Italy	IG: 20 (7) CG: 20 (7)	IG: 69.9 (6.42) CG: 66.4 (9.32)	IG: 27 m (7) CG: 28 m (8)	IG: 16 in stage II CG: 15 in stage II	IG: 11(5)[b] CG: 8.5 (7.5)[b]	IG: physiotherapy program CG: usual exercise	IG: transfers + body posture + reaching and grasping + balance + gait CG: exercise of upper limbs + lower limbs + spine + balance + breathing	12 w-2 sxw (60 min)
Duncan and Earhart[41] (2012)	United States	IG: 26 (11) CG: 26 (11)	IG: 69.3 (1.9)[b] CG: 69.0 (1.5)[b]	IG: 5.8 (1.1)[b] CG: 7.0 (1.0)[b]	IG: 2.6 (0.1)[b] CG: 2.5 (0.1)[b]	IG: 44.5 (2.3)[b] CG: 48.0 (1.8)[b]	IG: Argentine tango CG: usual care	IG: 5-min greeting and practice + 10-min warm–up + 10-min new steps + 15-min music/rhythmic training + 17-min amalgamation and encapsulation + 3-min close	48 sesions-2 sxw (60 min)

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Ebersbach et al[42] (2010)	Germany	IG1: 20 (13) IG2: 19 (12) CG: 19 (11)	IG1: 67.1 (3.6) IG2: 65.5 (9.0) CG: 69.3 (8.4)	IG1: 6.1 (3) IG2: 7.8 (4.4) CG: 7.4 (5.9)	IG1: 2.8 (0.37) IG2: 2.6 (0.4) CG: 2.5 (0.7)	IG1: 21.1 (6.3) IG2: 18.5 (5.8) CG: 19.1 (9.7)	IG1: Lee Silverman voice treatment IG2: Nordic walking CG: home-based exercise	IG1: whole-body movements + stretching + goal-directed activities of daily living IG2: warm-up + practicing Nordic walking + cool-down CG: stretching + high-amplitude movements + active work for muscular power and posture	IG1: 4 w-4 sxw (60 min) IG2: 8 w-2 sxw (60 min) CG: 1 s (60 min)
Fisher et al[43] (2008)	United States	IG1: 10 (4) IG2: 10 (5) CG: 10 (2)	IG1: 64.0 (14.5) IG2: 61.5 (9.8) CG: 63.1 (11.5)	IG1: 14.7 m (9.9) IG2: 8.8 m (7.9) CG: 17.7 m (13.3)	IG1: 1.9 (0.5) IG2: 1.9 (0.3) CG: 1.9 (0.3)	IG1: 27.6 (10.3) IG2: 30.5 (8.7) CG: 27.6 (7.3)	IG1: treadmill walking IG2: physical therapy CG: zero-intensity group	IG1: treadmill at 10% BWS and 3.0 METS—75% AAMHR IG2: passive range of motion and stretching + active range of motion + balance + gait + resistance + functional activities and transitional movement CG: education class	8 w-3 sxw (45 min) 8 w-6 sxw (60 min)
Furnari et al[44] (2017)	Italy	IG1: 19 (8) IG2: 19 (9)	IG1: 71.5 (11.7) IG2: 77.7 (8.3)	NA	IG1: 3.1 (0.9) IG2: 2.2 (0.5)	IG1: 32.36 (15.46) IG2: 30.15 (12.70)	IG1: robot-assisted gait training IG2: overground gait training	IG1: 30-min robot-assisted gait training at 2.2-2.5 km/h + 30-min conventional exercise program IG2: 30-min proprioceptive neuromuscular facilitation + 30-min conventional exercise program	4 w-6 sxw (60 min)
Galli et al[45] (2016)	Italy	IG1: 25 (11) IG2: 25 (13)	IG1: 68.8 (6.9) IG2: 66.4 (9.7)	IG1: 9.9 (NA) IG2: 8.1 (NA)	IG1: 1.5-3 IG2: 2-4	IG1: 39 (34-45) IG2: 50 (43-53)	IG1: robot-assisted gait training IG2: overground gait training	IG1: 45-min robot-assisted gait training at 2.2-2.5 km/h + 135-min occupational therapy for upper limbs IG2: 45-min treadmill + 135-min occupational therapy for upper limbs	4 w-5 sxw (180 min)
Ganesan et al[46] (2014)	India	IG1: 20 (5) IG2: 20 (5) CN: 20 (4)	IG1: 57.7 (10.3) IG2: 57.6 (9.1) CN: 59.1 (6.8)	IG1: 4.9 (3.1) IG2: 5.7 (3.9) CN: 5.5 (3.4)	IG1: 17 in stage II IG2: 17 in stage II CN: 16 in stage II	IG1: 30.70 (5.04) IG2: 31.95 (4.26) CN: 30.15 (3.88)	IG1: walking IG2: treadmill walking CN: usual care	IG1: 5-min warm-up + 30-min walking in straight path + turning and arm swinging strategies + 5-min cool-down IG2: 5-min warm-up + 30-min treadmill walking 20% BWS + 5-min cool-down	4 w-4 sxw (30 min)
Gao et al[47] (2014)	China	IG: 37 (14) CG: 39 (12)	IG: 69.54 (7.32) CG: 68.28 (8.53)	IG: 9.15 (8.58) CG: 8.37 (8.24)	IG: 19 in stage II CG: 12 in stage II	IG: 31.86 (11.49) CG: 30.62 (9.90)	IG: tai chi group CG: usual care	IG: 24-form Yang style tai chi exercise	12 w-3 sxw (60 min)

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Gobbi et al[48] (2009)	Brazil	IG1: 21 (11) IG2: 13 (8)	IG1: 67 (9) IG2: 69 (8)	NA	IG1: 2 (1) IG2: 2 (1)	IG1: 21 (12) IG2: 31 (14)	IG1: multimode exercise IG2: adaptative program	IG1: aerobic exercise + flexibility + strength + motor coordination + balance IG2: flexibility + strength + motor coordination + balance	IG1: 24 w-3 sxw (60 min) IG2: 24 w-1 sxw (60 min)
Hackney et al[49] (2007)	United States	IG: 9 (3) CG: 10 (4)	IG: 72.6 (2.2)[b] CG: 69.6 (2.1)[b]	IG: 6.2 (1.5)[b] CG: 3.3 (0.5)[b]	IG: 2.3 (0.7)[b] CG: 2.2 (0.6)[b]	IG: 30.6 (1.3)[b] CG: 28.2 (1.2)[b]	IG: Argentine tango CG: exercise classes	IG: postural stretches + balance + tango-style walking + footwork patterns/experimentation with timing of steps to music CG: 40-min breathing/stretching and resistance/dexterity exercises + 10-min stretching and strengthening exercises	13 w-21 s (60 min)
Hackney and Earhart[50] (2008)	United States	IG: 13 (2) CG:13 (3)	IG: 64.9 (8.3) CG: 62.6 (10.2)	IG: 8.7 (4.7) CG: 5.5 (3.3)	IG: 2.0 (1.5-2.1)[b] CG: 2.0 (2.0-2.0)[b]	IG: 25.5 (21.5-32.8)[b] CG: 24.0 (17.8-28.3)[b]	IG: tai chi CG: no intervention	IG: Yang Short Style of Cheng Manching	13 w-2 sxw (60 min)
Hackney and Earhart[51] (2009)	United States	IG1: 17 (6) IG2: 14 (3) CG: 17 (5)	IG1: 66.8 (2.4)[b] IG2: 68.2 (1.4)[b] CG: 65.5 (2.8)[b]	IG1: 9.2 (1.5)[b] IG2: 6.9 (1.3)[b] CG: 5.9 (1.0)[b]	IG1: 2.0 (0.2)[b] IG2: 2.1 (0.1)[b] CG: 2.2 (0.2)[b]	IG1: 26.9 (2.5)[b] IG2: 27.6 (2.0)[b] CG: 27.4 (2.4)[b]	IG1: waltz/foxtrot lessons IG2: tango lessons CG: no intervention	NA	13 w-2 sxw (60 min)
Kurt et al[52] (2018)	Turkey	IG: 20 (9) CG: 20 (7)	IG: 62.41 (6.76) CG: 63.61 (7.18)	NA	IG: 9 in stage II CG: 11 in stage II	IG: 30.09 (4.88) CG: 28.06 (5.37)	IG: water Ai Chi exercises CG: land-based exercises	IG: 15-min warm-up + 30-min 16 different movements of Ai Chi + 15-min cool-down CG:10-min warm-up + 10-min stretching + 30-min balance and gait training + 10-min cool-down	5 w-5 sxw (60 min)
Lee et al[53] (2018)	Republic of Korea	IG: 25 (15) CG: 16 (9)	IG: 65.8 (7.2) CG: 65.7 (6.4)	IG: 4.5 (3.3) CG: 4.4 (3.0)	IG: 10 in stage II CG: 5 in stage II	IG: 14.8 (6.7) CG: 11.9 (3.1)	IG: Qigong and meridian therapy CG: usual care	IG: 15-min relaxing the meridians + 30-min circulating Qi + 15-min stabilizing Qi	8 w-2 sxw (60 min)
Li et al[54] (2012)	United States	IG1: 65 (20) IG2: 65 (27) CG: 65 (26)	IG1: 68 (9) IG2: 69 (8) CG: 69 (9)	IG1: 8 (9) IG2: 8 (9) CG: 6 (5)	IG1: 34 in stage II IG2: 27 in stage II CG: 28 in stage II	IG1: 15.28 (5.59) IG2: 15.32 (6.04) CG: 15.06 (6.17)	IG1: tai chi IG2: resistance training CG: low-intensity exercise	IG1: 6-tai chi movements into 8-form routine IG2: strengthening + resistance CG: stretching + breathing	24 w-2 sxw (60 min)

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Meng et al[55] (2016)	United States	IG1: 14 (5) IG2: 13 (2) CG: 10 (6)	IG1: 71.6 (6.6) IG2: 71.2 (6.5) CG: 74.9 (8.3)	IG1: 6.6 (4.4) IG2: 6.9 (6.3) CG: 5.9 (6.2)	IG1: 2.2 (0.6) IG2: 2.2 (0.7) CG: 2.1 (0.7)	IG1: 32.9 (12.0) IG2: 28.15 (11) CG: 27.6 (7.8)	IG1: power training IG2: yoga CG: health education classes	IG1: loads on 11 pneumatic machines IG2: Vinyasa Yoga poses CG: lifestyle modification + medication + therapy/exercise + nutrition/long-term care	IG1: 12 w-2 sxw (45-60 min) IG2: 12 w-2 sxw (60 min) CG: 12 w-1 sxm (60 min)
Miyai et al[56] (2002)	Japan	IG1: 11 (6) IG2: 9 (4)	IG1: 69.5 (1.9)[b] IG2: 69.8 (1.5)[b]	IG1: 4.1 (0.8)[b] IG2: 4.5 (0.7)[b]	IG1: 2.9 (0.1)[b] IG2: 2.8 (0.1)[b]	IG1: 18.5 (1.2)[b] IG2: 18.6 (1.4)[b]	IG1: treadmill walking IG2: physical therapy	IG1: 45-min treadmill with 0%-20% BWS and 0.5-3.0 km/h +45-min occupational therapy and transfers IG2: 45-min general conditioning + range of motion + ADL/gait training + 45-min occupational therapy and transfers	4 w-3 sxw (90 min)
Modugno et al[57] (2010, al año-T1)	Italy	IG: 10 (5) CG: 10 (5)	IG: 63.2 (1.13)[b] CG: 62 (1.58)[b]	IG: 9.4 (1.1)[b] CG: 10 (1.8)[b]	IG: 3.5 (0.17)[b] CG: 3 (0.22)[b]	IG: 23.5 (3.01)[b] CG: 26.9 (4.86)[b]	IG: physiotherapy CG: therapeutic theatre	IG: 10-min warm-up + 15-min stretching + 15-min postural exercise + 20-min gait + 15-min balance + 15-min relaxation CG: 20-min vocal warm-up + 40-min preparation of the scene + 5-h staging	IG: 3 y-3 sxw (120-180 min) CG: 3 y-2-4 sxm (360 min)
Mollinedo-Cardalda et al[58] (2018)	Spain	IG1: 13 (8) IG2: 13 (9)	IG1: 62.85 (9.75) IG2: 66.0 (13.14)	IG1: 5.77 (3.39) IG2: 5.69 (4.4)	IG1: 2.08 (0.49) IG2: 2.00 (0.82)	IG1: 29.55 (11.26) IG2: 31.54 (11.84)	IG1: Pilates IG2: physical activity program	IG1: 10-min warm-up + 45-min exercise with medium-resistant Theraband and 0.5-kg ankle/wristbands + 5-min cool-down IG2: 10-min warm-up + 45-min aerobic/strength/flexibility/articular mobility/coordination exercises + 5-min cool-down	12 w-2 sxw (60 min)

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

		Population Characteristics					Intervention characteristics		
Study (Year)	Country	Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Monticone et al[59] (2015)	Italy	IG: 35 (11) CG: 35 (13)	IG: 74.1 (6.0) CG: 73.4 (7.0)	IG: 15.7 (2.6) CG: 15.3 (3.0)	IG: 20 in stage III CG: 22 in stage III	IG: 83.0 (15.3) CG: 83.0 (14.3)	IG: motor, cognitive, and ergonomic training CG: resistance and velocity training	IG: task-oriented + balance + gait exercises + neuropsychological training + ADLs exercises CG: neuromotor techniques, articular mobilization, strengthening and stretching, balance and walking exercises	IG: 8 w-5 sxw (90 min) + 30 min xw psychologist + 30 min xw OT CG: 8 w-5 sxw (90 min)
Morris et al[60] (2015)	Australia	IG1: 70 (28) IG2: 69 (23) CG: 71 (19)	IG1: 67.4 (10.4) IG2: 68.4 (9.9) CG: 67.9 (8.4)	IG1: 7.2 (6.2) IG2: 6 (5.5) CG: 6.9 (5.2)	IG1: 22 in stage II IG2: 17 in stage II CG: 17 in stage II	IG1: 14.6 (5,9) IG2: 14.9 (6.3) CG: 16.2 (6.5)	IG1: progressive resistance strength IG2: movement strategy training CG: life skills program	IG1: functional resistance with Theraband and BW + education to prevent falls IG2: strategies to prevent falls, improve mobility and balance during functional tasks + education to prevent falls CG: social activities, practical advice, information sessions, and group discussion	8 w-1 sxw (120 min)+ 120 min 1 sxw of home exercise
Nadeau et al[61] (2014)	Canada	IG1: 12 (4) IG2: 11 (1) IG3: 11 (2)	IG1: 64.0 (6.6) IG2: 60.1 (6.8) IG3: 63.4 (5.6)	NA	IG1: 1.92 (0.20) IG2: 1.92 (0.20) IG3: 1.86 (0.23)	IG1: 29.1 (11.8) IG2: 21.9 (5.5) IG3: 17.9 (6.6)	IG1: speed treadmill group IG2: mixed treadmill group IG3: low intensity routines	IG1: 5-min warm-up + 45-min treadmill at 80%-100% preferential speed + 5-min cool-down IG2: 5-min warm-up + 45-min treadmill at +0.2 km/h + 5-min cool-down IG3: tai chi + Latin dance + resistance band exercise + coordination movements	24 w-3 sxw (60 min)
Paccheitti et al[62] (2000)	Italy	IG1: 16 (4) IG2: 16 (5)	IG1: 62.5 (5) IG2: 63.2 (5)	IG1: 4.8 (3) IG2: 5.2 (2)	NA	IG1: 40.2 (7.7) IG2: 40.7 (7)	IG1: music therapy IG2: physical therapy	IG1: 10-min entrance and interview + 10 min and visualization + 15- to 20-min choral singing and facial expression, breathing, and voice exercises + 30-min rhythmic movements + 30-40 improvisation + 20- to 30-min free body expression + 10-min conversation IG2: passive stretching exercises + motor tasks + balance + movement strategies	IG1: 13 w-1 sxw (120 min) IG2: 8 w-1 sxw (90 min)

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Perez de la Cruz[63] (2017)	Spain	IG1: 15 (NA) IG2: 15 (NA)	IG1: 66.80 (5.27) IG2: 67.53 (9.89)	IG1: 6.2 (2.54) IG2: 6.7 (3.22)	IG1: 2.82 (0.22) IG2: 2.66 (1.02)	IG1: 36.4 (16.53) IG2: 36.40 (15.16)	IG1: aquatic Ai Chi IG2: dry land therapy	IG1: 35-min Ai Chi program + 10-min calm down IG2: 10-min warm-up + 25-min strength training and aerobic exercises + 10-min cool-down	10 w-2 sxw (45 min)
Picelli et al[64] (2012)	Italy	IG1. 17 (NA) IG2: 17 (NA)	68.3 (NA)	7.5 (NA)	3.45 (NA)	IG1: 46.31 (6.65) IG2: 47.20 (7.93)	IG1: robotic training IG2: physical therapy	IG1: 40-min robot-assisted gait training at 1.3-1.6 km/h IG2: stretching, mobilization and coordination	4 w-3 sxw (40 min)
Picelli et al[65] (2015)	Italy	IG1: 33 (7) IG2: 33 (11)	IG1: 68.2 (9.2) IG2: 69.7 (7.2)	IG1: 7.5 (5.6) IG2: 8.3 (4.1)	NA	IG1: 38 (32-43)[b] IG2: 40 (35-42)[b]	IG1: robotic training IG2: balance training	IG1: 40-min robot-assisted gait training at 1.0-2.0 km/h IG2: feed-forward postural control + feed-back postural control + postural adjustment	4 w-3 sxw (45 min)
Poliakoff et al[66] (2013) T2	United Kingdom	IG: 12 (3) CG: 10 (2)	IG: 68.8 (48-77) CG: 66.6 (49-78)	IG: 7.90 (4.6-16.7) CG: 4.58 (0.25-16)	NA	IG: 18.5 (6.2) CG: 15.2 (4.3)	IG: exercise group CG: usual care	IG: cardiovascular activity, including treadmill, recumbent bikes, bikes, cross-trainers and rowers + gait and agility	10 w-2 sxw (60 min)
Romenets et al[67] (2015)	Canada	IG: 18 (6) CG: 15 (8)	IG: 63.2 (9.9) CG: 64.3 (8.1)	IG: 5.5 (4.4) CG: 7.7 (4.6)	IG: 1.7 (0.6) CG: 2.0 (0.5)	IG: 20.7 (10.1) CG: 27.5 (14.5)	IG. Argentine tango CG: control	IG: review of previous class + new step or elements+ improvisation activities + standard footwork exercises	12 w-2 sxw (60 min)
SSage and Almeida[68] (2009)	Canada	IG1: 18 (6) IG2: 13 (7) CG: 15 (8)	IG1: 64.2 (10.3) IG2: 65.1 (9.3) CG: 68.6 (8.7)	IG1: 4.7 (4.9) IG2: 3.2 (2.9) CG: 2.5 (2.2)	NA	IG1: 22.47 (5.8) IG2: 22.2 (8.1) CG: 21.8 (7.2)	IG1: sensory attention-focused exercise IG2: low-limb aerobic training CG: control group	IG1: 20- to 30-min nonaerobic gait exercises + 20- to 30-min sensory attention exercises with Therabands IG2: 5-min warm-up + 20-min lower limb aerobic training on ellipticals at 60%-75% HR + 5-min cool-down	12 w-3 sxw (30 min)
Sale et al[69] (2013)	Italy	IG1: 10 (4) IG2: 10 (5)	IG1: 70.27 (9.81) IG2: 68.42 (9.41)	IG1: 8.41 (4.99) IG2: 8.72 (4.74)	IG1: 2.5-3.5 IG2: 2.5-3.5	IG1: 53.57 (14.74) IG2: 56.17 (13.86)	IG1: robot-assisted gait IG2: treadmill rehabilitation	IG1: 45-min robot-assisted gait at 1.5-2.5 km/h + 135-min OT for upper limbs IG2: 45-min treadmill + 135-min OT for upper limbs	4 w-5 sxw (180 min)

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Schenkman et al[70] (2012)	United States	IG1: 41 (15) IG2: 39 (15) CG: 41 (15)	IG1: 63.4 (11.2) IG2: 64.5 (10.0) CG: 66.3 (10.1)	IG1: 3.9 (4.2) IG2: 4.9 (3.7) CG: 4.5 (3.8)	IG1: 2.2 (0.5) IG2: 2.3 (0.4) CG: 2.3 (0.4)	IG1: 24.4 (9.1) IG2: 24.3 (10.5) CG: 25.9 (8.9)	IG1: supervised aerobic exercise IG2: flexibility/balance/function exercise CG: home-based exercise	IG1: 5- to 10-min warm-up + 30-min exercise at 65%-80% of HRmax + 5- to 10-min cool-down. IG2: flexibility/balance/functional exercise CG: home-based exercise based on fitness counts	IG1 and IG2: 16 w- 5-7 sxw (45-50 min) CG: 16 m-1 supervised-sxm (45-50 min) + 5-7 s/w (45-50 min)
Schenkman et al[71] (2018)	United States	IG1: 43 (21) IG2: 45 (18) CG: 40 (16)	IG1: 64 (9) IG2: 63 (10) CG: 64 (10)	IG1: 0.3 (0.1-1.3)[b] IG2: 0.3 (0.2-0.8)[b] CG: 0.4 (0.1-0.8)[b]	IG1: 31 in stage II IG2: 32 in stage II CG: 32 in stage II	IG1: 17 (7) IG2: 16 (7) CG: 17 (7)	IG1: high-intensity treadmill IG2: moderate-intensity treadmill CG: usual care	IG1: 5- to 10-min warm-up + 30-min high- intensity treadmill exercise at 80%-85% HRmax + 5-to 10-min cool-down IG2: 5- to 10-min warm-up + 30-min moderate-intensity treadmill exercise 60%-65% HRmax + 5- to 10-min cool-down	26 w-4 sxw (50 min)
Schlenstedt et al[72] (2015)	Germany	IG1: 17 (5) IG2: 15 (6)	IG1: 75.7 (5.5) IG2: 75.7 (7.2)	IG1: 10.1 (6.0) IG2: 9.3 (7.9)	IG1: 2.8 (0.26) IG2: 2.7 (0.4)	IG1: 22.6 (9.5) IG2: 20.3 (6.1)	IG1: resistance training IG2: balance training	IG1: 10-min warm-up + 50-min strength of lower limbs IG2: 10-min warm-up + 50-min stance and gait tasks	7 w-2 sxw (60 min)
Shulman et al[73] (2013)	United States	IG1: 23 (7) IG2: 22 (6) IG3: 22 (4)	IG1: 66.1 (9.7) IG2: 65.8 (11.5) IG3: 65.3 (11.3)	IG1: 5.9 (3.9) IG2: 6.3 (3.5) IG3: 6.3 (4.0)	IG1: 19 in stage II IG2: 18 in stage II IG3: 16 in stage II	IG1: 30.3 (9.8) IG2: 31.6 (9.2) IG3: 34.5 (10.7)	IG1: higher-intensity treadmill training IG2: lower intensity treadmill training IG3: stretching and resistance training	IG1: increasing 5 min, 0.2 km/h and 1% incline every week to reach 30 min at 70%-80% HRR IG2: 0% incline increasing 5 min every 2 wk to reach 50 min at 40%-50% HRR IG3: strengthening of the lower body + stretching of the upper and lower body	12 w-3 sxw IG1: 30 min IG2: 50 min IG3: NA

(*continues*)

Table 1. Characteristics of the Included Studies[a] (*Continued*)

Study (Year)	Country	Population Characteristics					Intervention characteristics		
		Sample Size (No. Women)	Age (Mean ± SD), y	Duration of PD (Mean ± SD), y	Basal H&Y (Mean ± SD)	Basal UPDRS (Mean ± SD) or CI	PA Intervention	PA Characteristics	Dose
Silva-Batista et al[74] (2016)	Brazil	IG1: 13 (3) IG2: 13 (3) CG: 13 (4)	IG1: 64.1 (9.1) IG2: 64.2 (10.6) CG: 64.2 (8.3)	IG1: 9.6 (3.9) IG2: 10.5 (4.1) CG: 10.7 (6.1)	IG1: 2.5 (0.5) IG2: 2.5 (0.4) CG: 2.5 (0.4)	IG1: 43.7 (13.4) IG2: 45.1 (8.2) CG: 43.4 (8.6)	IG1 and IG2: resistance training CG: educational group	IG1: 10-min warm-up + resistance exercises with load/resistance progressively increased IG2: 10-min warm-up + resistance exercises with load/resistance and instability progressively increased CG: bingo games and education	IG1 and IG2: 12 s-2 sxw (50 min) CG: 12 w-1 sxw (60 min)
Solla et al[75] (2019)	Italy	IG: 10 (4) CG: 10 (3)	IG: 67.8 (5.9) CG: 67.1 (6.3)	IG: 4.4 (4.5) CG: 5 (2.9)	IG: 2.1 (0.6) CG: 2.3 (0.4)	IG:13.0 (7.23) CG: 14.67 (7.02)	IG: Sardinian folk dance CG: usual care	IG: 30-min warm-up + 50-min Sardinian folk dance +10-min cool-down	12 w-2 sxw (90 min)
van der Kolk et al[79] (2019)	The Netherlands	IG: 65 (23) CG: 65 (27)	IG: 59.3 (8.3) CG: 59.4 (9.3)	IG: 3.4 (1.3-7.3) CG: 3.2 (1.6-6.8)	IG: 61 in stage II CG: 63 in stage II	IG: 19.4 (1.8) CG: 17.4 (1.8)	IG: aerobic exercise CG: no intervention	IG: 30-min on stationary cycle at 50%-70% of HRR + 15-min cool-down CG: stretching + flexibility + relaxation exercises	IG: 24 w-3 sxw (30-45 min) CG: 24 w-3 sxw (30 min)
Volpe et al[76] (2013)	Italy	IG: 12 (5) CG: 12 (6)	IG: 61.6 (4.5) CG: 65.0 (5.3)	IG: 9.0 (3.6) CG: 8.9 (2.5)	IG: 2.2 (0.4) CG: 2.2 (0.4)	IG: 24.58 (3.87) CG: 23.92 (3.50)	IG: Irish dance CG: physiotherapy	IG: 10-min warm-up + 70-min Irish dance + 10-min cool-down CG: 10-min warm-up + 50-min strength /balance/ postural reeducation + 20-min gait training + 10-min cool-down	24 w-1 sxw (90 min)
Xiao and Zhuang[77] (2016)	China	IG1: 48 (14) IG2: 48 (15)	IG1: 66.52 (2.13)[c] IG2: 68.17 (2.27)[c]	IG1: 6.15 (2.63)[c] IG2: 5.45 (3.61)[c]	IG1: 2.1 (0.23)[c] IG2: 2.2 (0.21)[c]	IG1: 26.9 (2.05)[c] IG2: 27.4 (2.51)[c]	IG1: daily walking IG2: Baduanjin Oigong	IG1: daily walking IG2: 8 distinct movement routines of Baduanjin Qiong	IG1: 24 w-7 sxw (30 min) IG2: 24 w-4 sxw (12-15 min) + 7 s/w as CG
Zhang et al[78] (2015)	China	IG1: 20 (7) IG2: 20 (9)	IG1: 66 (11.80) IG2: 64.35 (10.53)	IG1: 6.8 (5.43) IG2: 4.85 (3.72)	IG1: 7 in stage II IG2: 6 in stage II	IG1: 18.50 (6.20) IG2: 16.35 (7.38)	IG1: tai chi IG2: multimodal exercise training	IG1: Yang style 24-posture short form tai chi IG2: core muscle training + 10-min cross-obstacle training + standing on ankle joint + 10-min cycle ergometer	12 w-2 sxw (60 min)

Abbreviations: ADL, activities of daily living; AAMHR, age-appropriate maximal heart rate; BW, body weight; BWS, body weight support; CI, confidence interval; CG, control group; DNI, dynamic neurocognitive imagery; HR, heart rate; HRmax, maximunm heart rate; HRR, heart rate reserve; H&Y, Hoehn and Yahr stage; IG, intervention group; METS, metabolic equivalents; NA, not available; OT, occupational therapy; PA, physical activity; PD, Parkinson Disease; UPDRS, Unified Parkinson's Disease Rating Scale.

[a]All values are mean (SD), unless otherwise indicated.

[b]Median (interquartile range).

[c]Median (standard error).

"high risk of bias" when there was at least 1 domain classified as "high risk" or several domains with "some concerns."

Grading the Quality of Evidence

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)[17] tool was used to evaluate the quality of the evidence and make recommendations. Each outcome obtained a high, moderate, low, or very low evidence value, depending on the design of the studies, risk of bias, inconsistency, indirect evidence, imprecision, and publication bias.

Literature search, data extraction, risk of bias assessment, and grading the quality of evidence were independently performed by 2 researchers (C.A.B. and I.C.R.), and disagreements were resolved by consensus or involving a third researcher (V.M.V.).

Data Synthesis and Analysis

To perform the meta-analysis, physical exercise interventions were classified into 9 categories: endurance (aimed at increasing heart rate and energy expenditure), resistance (aimed at increasing muscle strength and muscle power), combined (including only aerobic exercise and resistance training), stretching (aimed at increasing muscle's elasticity and achieving comfortable muscle tone), dance (interventions with target balance and complex gait tasks in coordination with music), balance (aimed at improving postural reactions by strengthening of muscles that help keep you upright), body weight–supported (aimed at maintaining the lower limb trajectories, while increasing the motor activation and motor function by reducing the patient's weight) alternative exercises ([tai chi, yoga, Qui-Gong, and Ai-Chi] understood as a modality of exercise that combines body movement, mental focus, and controlled breathing for improving strength, balance, and flexibility), and sensorimotor training (aimed at improving the neuromuscular system by the emphasis on postural control and progressive challenges to the sensorimotor system, using aerobic, relaxation, postural and stretching exercises, and gait and balance training) including endurance, and sensorimotor training not including endurance.

Before conducting the network meta-analysis, we examined the statistical power of the interventions to find differences between groups by using the baseline mean in the motor part of the UPDRS, the sample size, and the common standard deviation for both groups. For studies including more than 1 intervention group, estimates were calculated for each comparison included in this network meta-analysis. In addition, these estimates were also calculated for studies reporting their procedures for sample size determination.

The included studies were summarized narratively in an ad hoc table describing the types of direct and indirect comparisons. We conducted our network meta-analysis according to the steps outlined in the PRISMA-NMA statement: (i) the strength of the evidence was assessed through a network geometry graph in which the number of participants in trials was represented by the size of the node, and the thickness of the continuous line to connect nodes is proportional to the sample size in trials that directly compared the 2 interventions.[18] (ii) Consistency was assessed by checking whether the intervention effects estimated from direct comparisons were consistent with those estimated by indirect comparisons; consequently, the Wald test and the side-splitting assessment were used. (iii) Comparative evaluation of the intervention effect was assessed by performing a standard meta-analysis for each direct comparison between 2 physical exercise interventions using the random effect DerSimonian-Laird method.[19] These results were displayed by creating both forest plots and a league table. In addition, statistical heterogeneity was analyzed by calculation of the I^2 statistic. According to the values of I^2,[14] the heterogeneity was considered as not important (0%-40%), moderate (30%-60%), substantial (50%-90%), or considerable (75%-100%), and the corresponding p values were also considered. Finally, to determine the size and clinical relevance of heterogeneity, the τ^2 statistic was calculated and interpreted as low (lower than 0.04), moderate (0.04-0.14), and as substantial (0.14-0.40).[20] (iv) The probability of each physical activity intervention being the most effective was presented graphically using cumulative rankograms.[21] In addition, the surface under the cumulative ranking curve (SUCRA) was estimated for each intervention, which involves the assigning of a numerical value between 0 and 1 in such a way that the best intervention obtained a value for SUCRA closest to 1 and the worst intervention obtained a value closest to 0.[18] (v) Small study effect and publication bias was estimated using Egger's test.[22] (vi) Sensitivity analyses were performed excluding studies one by one from the pooled estimates, in order to evaluate whether any particular study significantly modified the original summary estimate. Finally, (vii) meta-regression analyses were conducted to examine the influence of the duration of the intervention (weeks) and the weekly (min) time spent on sessions. Meta-regressions were performed to estimate the effect of intervention groups versus control groups, including at least 6 studies.

We used the frequentist random effects multivariate network meta-analysis to synthesize the evidence for exercise interventions and to achieve a ranking of treatments. All analyses were conducted in Stata 15.0 (Stata, College Station, Texas). The following methodological issues were pointed out: (i) when studies involved data on ON (when there is a successful control of motor symptoms) and OFF (when medication is not optimally effective)[23] PD motor symptoms, only data on ON motor symptoms were included in the pooled estimates; (ii) when studies provided 2 or more end point measurements over time, the closest one to the most frequently reported was considered in this meta-analysis; and (iii) when studies included follow-up without intervention measurements, these were not included in this meta-analysis.

RESULTS

The search retrieved 12 496 studies, of which 56 were included in this network meta-analysis.[24-79] (Figure 1; see Supplemental Digital Content Figure 1, available at: http://links.lww.com/JGPT/A76). They included 125 intervention groups with 2038 participants, and 49 control groups with 702 participants. Their mean age was between 57.6 and 77.7 years and the duration of PD from the diagnosis ranged from 2.5 to 15.7 years. Physical exercise program duration varied from 2 weeks to 3 years (involved 1-5 sessions per week, lasting between 120 and 180 minutes) (Table 1).

The number of intervention groups classified within each category was as follows: endurance, 31; resistance, 21; combined exercise, 3; balance, 3; dance, 7; alternative exercises, 19; body weight–supported interventions, 11; sensorimotor interventions including endurance, 8; and sensorimotor interventions not including endurance, 20.

Risk of Bias and Grade of Evidence

The overall risk of bias was high for all included studies. Regarding each domain, the studies recorded the following: for randomization process, 72.7% for some concerns and 9.1% for high risk of bias; for deviations from intended interventions, 95.5% as high risk of bias; for missing outcome data, all studies as low risk; for selection of the reported results, all studies as some concerns; and finally, for the measurement of the outcome domain, 97.7% were at low risk (see Supplemental Digital Content Table 2, available at: http://links.lww.com/JGPT/A77).

The quality of evidence, as assessed by the GRADE system, was moderate in 68% of the pairwise comparison studies, and low in 32% (see Supplemental Digital Content Table 3, available at: http://links.lww.com/JGPT/A78).

Statistical Power

The calculated statistical power of the interventions to find differences ranged from 3% to 100% (see Supplemental Digital Content Table 4, available at: http://links.lww.com/JGPT/A79).

Exercise and Motor Symptoms of PD

In pairwise analyses (Table 2), the highest mean difference was shown for alternative and endurance exercises versus control comparisons (−0.48; 95% confidence interval [CI], −0.82 to −0.13 and –0.36; 95% CI, −0.54 to −0.19, respectively). Moreover, dance interventions and sensorimotor interventions not including endurance, showed better results than sensorimotor interventions including endurance (0.87; 95% CI, 0.04-1.70 and 0.67; 95% CI, −0.06 to 1.27, respectively).

Finally, as shown in Table 2, the indirect effects of the network meta-analysis showed positive results for alternative (−0.52; 95% CI, −0.92 to −0.13), dance (−0.64; 95% CI, −1.24 to −0.05), endurance (−0.49; 95% CI, −0.82 to −0.15), resistance (−0.82; 95% CI, −1.23 to −0.41), sensorimotor interventions including endurance (−1.09; 95% CI, −1.68 to −0.50), and sensorimotor interventions not including endurance (−0.55; 95% CI, −0.90 to −0.21) versus control comparisons (Table 2).

Best Treatment Probabilities

The probability of being 1 of the 2 best treatments was 55% for sensorimotor interventions including endurance and 22% for balance programs. Furthermore, the highest SUCRA was for sensorimotor interventions including endurance (90%) and resistance programs (76%) (Figure 2; see Supplemental Digital Content Figure 2, available at: http://links.lww.com/JGPT/A80, and Supplemental Digital Content Table 5, available at: http://links.lww.com/JGPT/A81).

Sensitivity Analysis, Heterogeneity, and Publication Bias

The sensitivity analysis after removing one by one the studies from the pooled estimates showed that they were substantially modified only after removing the data from (i) Fisher et al,[43] from the body weight support interventions versus control groups and (ii) Duncan and Earhart,[41] from the dance interventions versus control groups (see Supplemental Digital Content Table 6, available at: http://links.lww.com/JGPT/A82).

Three direct comparisons showed moderate heterogeneity, which ranged from I^2= 45.5 to 57.8; τ^2 = 0.1297 to 0.1627 alternative exercises versus control; sensorimotor training including endurance versus body weight support, and sensorimotor training not including endurance versus control. Six direct comparisons showed substantial heterogeneity (body weight support vs control, body weight support vs endurance; dance vs control; resistance vs control; sensorimotor training not including endurance vs endurance; and sensorimotor training not including endurance vs sensorimotor training including endurance), which ranged from I^2 = 72.2 to 91.6, τ^2 = 0.2145 to 1.0538 (see Supplemental Digital Content Table 7, available at: http://links.lww.com/JGPT/A83).

Publication bias was found for the direct comparison of sensorimotor training not including endurance versus resistance (P = .066) (see Supplemental Digital Content Figure 3, available at: http://links.lww.com/JGPT/A84, and Supplemental Digital Content Table 8, available at: http://links.lww.com/JGPT/A85).

Meta-Regressions

Meta-regressions showed that only the duration of interventions influenced the relationship between dance interventions and UPDRS-III scores (see Supplemental Digital Content Table 9, available at: http://links.lww.com/JGPT/A86).

DISCUSION

This network meta-analysis aimed to provide evidence regarding the comparative effectiveness of exercise programs on motor symptoms of patients with PD as assessed using the motor part of the UPDRS. The results of this

Table 2. Pooled Mean Differences of Physical Activity on PD Motor Symptoms[a,b]

Control	−0.48 (−0.82 to −0.13)	NA	−0.70 (−1.79 to 0.40)	−0.06 (−0.44 to 0.32)	−0.10 (−0.67 to 0.48)	−0.36 (−0.54 to −0.19)	−0.88 (−0.82 to 0.06)	−0.39 (−0.87 to 0.08)	−0.27 (−0.62 to 0.07)
−0.52 (−0.92 to −0.13)	**Alternative**	NA	NA	−0.03 (−0.50 to 0.43)	NA	−0.10 (−0.46 to 0.26)	0.16 (−0.16 to 0.47)	−0.20 (−1.19 to 0.79)	0.21 (−0.41 to 0.84)
−0.71 (−1.80 to 0.37)	−0.19 (−1.32 to 0.94)	**Balance**	−0.24 (−0.72 to 0.24)	NA	NA	NA	0.05 (−0.64 to 0.75)	NA	NA
−0.35 (−0.87 to 0.17)	0.18 (−0.45 to 0.80)	0.37 (−0.69 to 1.42)	**BWS**	NA	NA	−0.53 (−1.48 to 0.43)	NA	NA	−0.13 (−0.77 to 0.50)
−0.42 (−1.25 to 0.41)	0.10 (−0.71 to 0.92)	0.29 (−1.06 to 1.65)	−0.07 (−1.04 to 0.90)	**Combined**	NA	NA	NA	NA	NA
−0.64 (−1.24 to −0.05)	−0.12 (−0.83 to 0.59)	0.07 (−1.16 to 1.30)	−0.29 (−1.08 to 0.49)	−0.22 (−1.24 to 0.80)	**Dance**	NA	NA	NA	**0.87 (0.04 to 1.70)**
−0.49 (−0.82 to −0.15)	0.04 (−0.43 to 0.50)	0.23 (−0.85 to 1.31)	−0.14 (−0.63 to 0.36)	−0.07 (−0.95 to 0.81)	0.16 (−0.52 to 0.83)	**Endurance**	−0.30 (−0.72 to 0.12)	NA	−0.28 (−0.80 to 0.24)
−0.82 (−1.23 to −0.41)	−0.29 (−0.81 to 0.22)	−0.10 (−1.17 to 0.96)	−0.47 (−1.07 to 0.13)	−0.40 (−1.31 to 0.51)	−0.17 (−0.89 to 0.54)	−0.33 (−0.79 to 0.12)	**Resistance**	NA	0.04 (−0.25 to 0.33)
−1.09 (−1.68 to −0.50)	−0.57 (−1.24 to 0.10)	−0.38 (−1.58 to 0.83)	−0.74 (−1.49 to 0.00)	−0.67 (−1.68 to 0.33)	−0.45 (−1.27 to 0.38)	−0.60 (−1.24 to 0.03)	−0.27 (−0.95 to 0.40)	**SMT + Endurance**	**0.67 (0.06 to 1.27)**
−0.55 (−0.90 to −0.21)	−0.03 (−0.51 to 0.45)	0.16 (−0.93 to 1.25)	−0.21 (−0.74 to 0.33)	−0.14 (−1.02 to 0.75)	0.09 (−0.58 to 0.75)	−0.07 (−0.404 to 0.31)	0.26 (−0.18 to 0.71)	0.54 (−0.04 to 1.11)	**SMT not endurance**

Abbreviations: BWS, body weight support; NA, not applicable; SMT, sensorimotor training.

[a]Upper right triangle gives the pooled mean differences from pairwise comparisons (column intervention relative to row), lower left triangle gives the pooled mean differences from the network meta-analysis (row intervention relative to column).

[b]Blodface indicates statistically significant results (95% interval confidence).

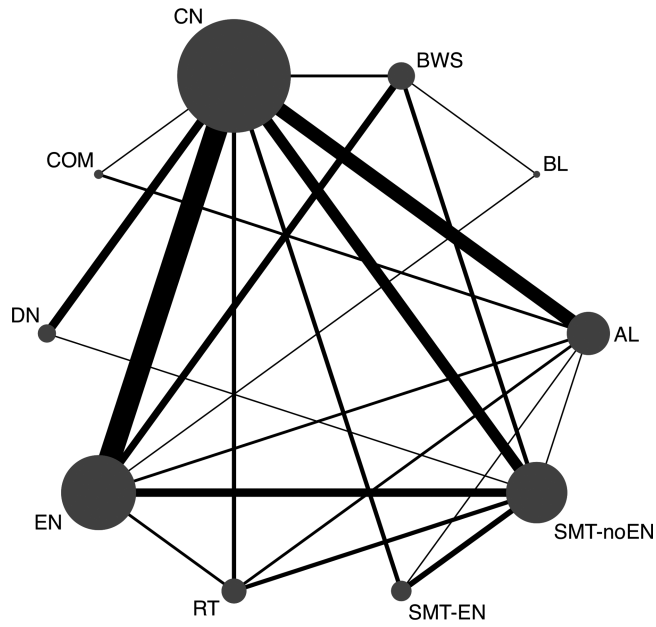

Figure 1. Network of available comparisons between physical activity interventions on PD motor symptoms measured by UPDRS. Size of node is proportional to number of trial participants, and thickness of continuous line connecting nodes is proportional to number of participants randomized in trials directly comparing the 2 treatments. AL indicates alternative; BL, balance; BWS, body weight support; CN, control; COM, combined exercise; DN, dance; EN, endurance; RT, resistance; SMT-EN, sensorimotor training with endurance; SMTnoEN, sensorimotor training without endurance.

network meta-analysis show that physical activity interventions are effective in the management of PD motor symptoms. The most effective physical activity interventions (in a decreasing order) were sensorimotor training including endurance, resistance, dance, sensorimotor training not including endurance, alternative exercise, and endurance training.

From our results, complex or multifaceted physical[9-80] activity programs that emphasize fine motor tasks such as holding a pencil, or gross motor tasks such as getting up from the bed, could improve walking, self-care, and other tasks by helping people modify and adjust how they perceive their movements. These aims could be achieved by those physical exercise programs including postural control and progressive challenges to the sensorimotor system, using aerobic, relaxation, postural, and stretching exercises, and gait and balance training. Dance, alternative exercise, resistance, endurance training, and

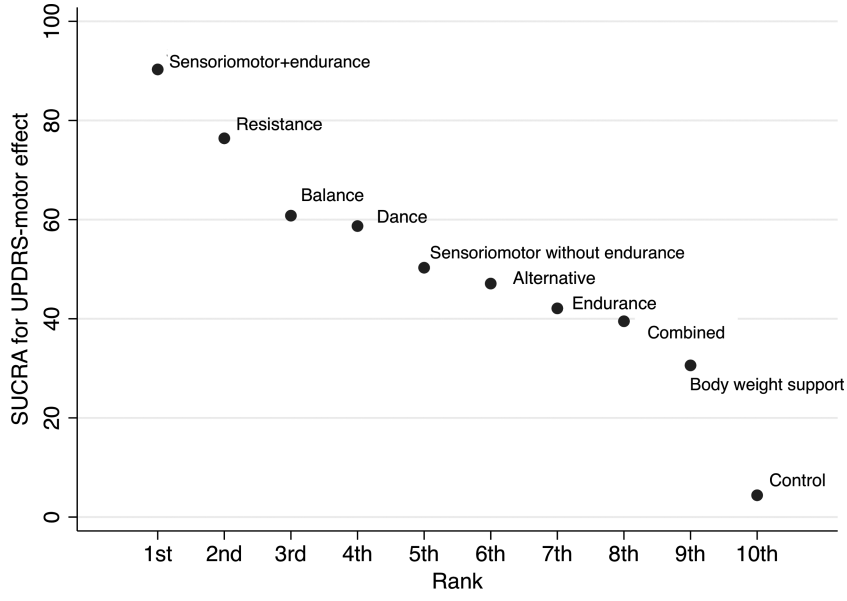

Figure 2. Surface under the cumulative ranking curve (SUCRA). UPDRS indicates Unified Parkinson's Disease Rating Scale.

sensorimotor training not including endurance and sensorimotor training including endurance could be included in this classification. The pharmacological treatment of PD motor symptoms is well-defined from the early stages of the disease, but gait and balance impairments persist and adverse effects of medication usually appear.[81] The absence of reported side effects of physical activity programs makes them a potentially useful adjunct to medication,[82] although patients might be closely followed as side effects could occur on the basis of patient's stage or severity of the health condition.

Previous research has reported positive effects of exercise on movement. In our study, most types of exercise confirmed these previous findings, although we did not find significant effects of balance, combined, and body weight–supported exercise programs, which seems not to adequately foster all the UPDRS-III dimensions. In addition, because the scarcity of studies and the width of the CI, the small, but significant, effect estimated for dance should cautiously be interpreted. These types of exercise are the less reported in the included studies, which could influence our data. In addition, owing to the increasing evidence of physical activity interventions in the treatment of PD motor symptoms, there is considerable heterogeneity among the intervention characteristics (intensity, frequency, and duration).[41] In addition, the scarcity of studies reporting the aforementioned interventions and the lack of information on their characteristics make difficult to firmly conclude about the effectiveness of these types of interventions.

Several mechanisms have been proposed to explain the benefits of exercise on PD motor symptoms. These exercises require the patient to respond to both cognitive and physical demands, incorporating specific movements involving multitask exigencies and motor skill learning.[41] Most physical activities include a visual or auditory cue, facilitating attention, balance, and rhythm on gait,[83] and reinforcing the neuronal circuits that contribute to lower limb movements.[84] In addition, some studies have hypothesized that exercise enhances the release of brain-derived neurotrophic factors and promotes neural repair and neuroplasticity.[61] The underlying mechanisms behind these are the increase in cerebral blood flow arising from these types of exercise.

Limitations

Some limitations encountered in this study were as follows. First, some studies did not report whether the patients were assessed in the ON- or OFF-medication state. Second, most studies included patients with PD in II to III H&Y stages, and this could limit the effect of the interventions. Third, although we have distinguished 9 exercise intervention types, it cannot be denied that there are some differences between each type of exercise classified into the same category, as well as their levels of intensity, frequency of delivery, and duration of programs. Fourth is the presence of a publication bias in the direct comparison of sensorimotor training not including endurance versus resistance. Thus, these data should be cautiously interpreted. Fifth, only studies reporting PD motor symptoms using the UPDRS scale have been included in this network meta-analysis and, therefore, some bias could not be avoided. Sixth, although data showed no influence of some intervention characteristics (duration of the intervention in weeks and weekly session time in minutes) on the effect size of intervention versus control groups in motor symptoms assessed by UPDRS-III, the meta-regression analyses were conducted only in those comparison subgroups, including 6 or more studies. Finally, the calculated statistical power of the studies was small in most, which could cause difficulties to find differences between groups. The use of meta-analysis reinforces the statistical power of individual studies.

CONCLUSION

Because of the high burden of disease attributable to PD, providing patients with effective approaches that could mitigate their motor symptoms and promote their independence in activities of daily living has become a priority. The results of this network meta-analysis allow us to conclude that physical activity interventions are an effective approach in the management of PD motor symptoms. Among the different intervention programs, sensorimotor training including endurance, resistance, and dance, and sensorimotor training not including endurance, alternative exercise, and endurance training seem to be the most effective physical activity interventions. This information is of use to clinicians prescribing exercise for mitigating motor symptoms in patients with PD, as well as to policy makers when designing new strategies to cope with the devastating consequences of PD.

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