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REVIEW

Guidelines on exercise testing and prescription for patients at different stages of Parkinson's disease

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Abstract

Background Exercise is highly recommended in patients with Parkinson's disease (PD). Exercise-induced amelioration of motor, non-motor, and drug-induced symptoms are widely known. However, specific guidelines on exercise testing and prescription in PD are lacking.

Objective This study reviews the literature on exercise-based approaches to the management of symptoms at each stage of the disease and evaluate: (1) the most suitable clinical exercise testing; (2) training programs based on testing outcomes and PD stage; (3) the effects of exercise on antiparkinsonian drugs and to suggest the most effective exercise–medication combination.

Methods A systematic search was conducted using the databases MEDLINE, Google Scholar and, Cochrane Library using "Parkinson's Disease AND Physical therapy", "Training AND Parkinson", "Exercise", "Exercise AND Drug" as key words. In addition, references list from the included articles were searched and cross-checked to identify any further potentially eligible studies.

Results Of a total of 115 records retrieved, 50 (43%) were included. From these, 23 were included under the rubric "exercise testing"; 20 focused on the effectiveness of different types of exercise in PD motor-functional symptoms and neuroprotective effects, throughout disease progression, were included under the rubric "training protocol prescription"; and 7 concern the rubric "interaction between exercise and medication", although none reported consistent results.

Conclusions Despite the lack of standardized parameters for exercise testing and prescription, all studies agree that PD patients should be encouraged to regularly train according to their severity-related limitations and their personalized treatment plan. In this manuscript, specific guidelines for tailored clinical testing and prescription are provided for each stage of PD.

Keywords Parkinson's disease · Physical activity · Training · Treatment · Guidelines

Introduction

Parkinson's disease (PD) affects 6 million people worldwide [1], making it one of the most common neurological syndromes derived from dopamine loss. Resting tremor, bradykinesia, rigidity, postural instability, and gait impairment are the main cardinal symptoms. Besides them, the psychological and emotional spheres are often involved, increasing disease severity [2]. While such diverse factors as aging, free radical toxicity, mitochondrial dysfunction, genetics, and environmental stressors can trigger PD onset [3], its etiology remains unknown.

Given the wide range of symptoms and inter-individual differences, a personalized and multidisciplinary approach to appropriate treatment planning is warranted. Currently, levodopa (L-DOPA) administration in the early PD stages is the

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gold standard therapy. Unfortunately, its chronic use induces dyskinesias accompanied by worsening of general health [4]. However, there is evidence from both human and animal models [5, 6] that, owing to its neuroprotective role [7], exercise can improve motor impairment and physical condition in PD patients regardless of the stage of the disease. To evaluate the most effective exercise-based treatments, patients are required to undergo clinical tests to identify disease stage-specific vital and motor parameters.

Currently, clear recommendations for the most suitable clinical exercise tests are lacking. Studies describe numerous tests that evaluate the domains affected by PD [38, 71], but the necessity to prescribe the correct exercise depending on the outcome of each test is still underestimated. Likewise, little is known about exercise programs in terms of frequency, intensity, time, and type (FITT) of intervention addressed to PD patients based on disease severity. High-intensity exercise and long-term therapy have been associated with greater benefits than low-intensity and medium- or short-term therapies [6, 8]. Moreover, a combination of mobility exercise, gait, and balance training [9], occupational therapy, cued exercises, high-intensity aerobic and resistance activities are recommended [10]. The effectiveness of training different muscle groups through various activities is increasingly recognized, along with the importance of supervision and motivation during preferred training activities. However, the most effective training program for PD patients remains a matter of debate.

Additionally, it is important to couple exercise and medication to maximize the beneficial effects over time and potentially counteract long-term drug side effects. While exercise training can be added to medications to manage disease symptoms and enhance their benefits [72], more rigorous investigations have to be conducted for cognitive function, daily living activities (ADL), and psychosocial variables. Even though exercise does not change greatly medications' effects, PD patients respond better during the "on" phase, or when they can move fluently thanks to the still circulating drug rather than during the "off" phase, when symptoms tend to reappear with compromised movements.

The present study aimed to review the PD literature on exercise testing, on personalized training programs and the impact of exercise on antiparkinsonian drug-treatment. The findings are summarized as indications for exercise-based non-pharmacological approaches to manage PD symptoms in each stage of the Hoehn and Yahr (H&Y) classification [11].

Methods

Following the PRISMA guidelines for systematic review of the literature [12], controlled clinical trials, systematic reviews, and works containing guidelines were identified and included by means of a computerized literature search in the Google Scholar, MEDLINE, Pubmed, and Cochrane Library electronic databases with the following keywords: Parkinson's disease AND physical therapy, training AND Parkinson, exercise, exercise AND drug. Furthermore, references and cross-references, bibliographies, citations of articles or publications were reviewed. The search strategy focused on (1) articles in English published from 1986 to 2019, (2) patients with PD and the respective exercise-based non-pharmacological prescribed treatment, (3) disease stage (H&Y classification), clinical tests, exercise prescription, type, intensity, and frequency of training, and drug administration. Selection criteria for clinical tests and training protocols were feasibility, usefulness, safety of each approach, in addition to compliance of subjects, and improvements of deficits described in the included works. Retrieved articles were grouped as follows: exercise testing, training protocol prescription and interaction between exercise and medication. The first two sections were further classified into three core areas: endurance, strength, and flexibility.

After excluding non-relevant articles, a total of 50 records were included (Fig. 1).

Results

Exercise testing

To obtain maximal benefits, the prescription of a personalized program upon clinical evaluation, functional capacity, mental health, and general fitness (e.g., cardiorespiratory fitness, muscular strength and endurance, flexibility) is suggested [13]. Moreover, given the chronic and progressive nature of PD, reassessment every 6–12 months to review the diagnosis and test program is recommended [11]. Albeit just for a few PD-related deficits, the general clinical tools for PD diagnosis are the older and simpler H&Y scale [14] and the newer Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [15]. However, in addition to scales and questionnaires, the most appropriate clinical test for examinations remain a matter of clinical judgment. Thus, the present review summarizes the most suitable exercise tests into the three main core areas of physical activity: endurance, strength, and flexibility.

Endurance assessment

Eleven articles were reviewed for endurance assessment. Generally, all studies included patients with mild-to-moderate disease (1–3 H&Y). Only one focused on advanced PD. Six researches tested patients under medication; in one study the patients were in off status, and four articles did not mention medication status. There was one randomized controlled

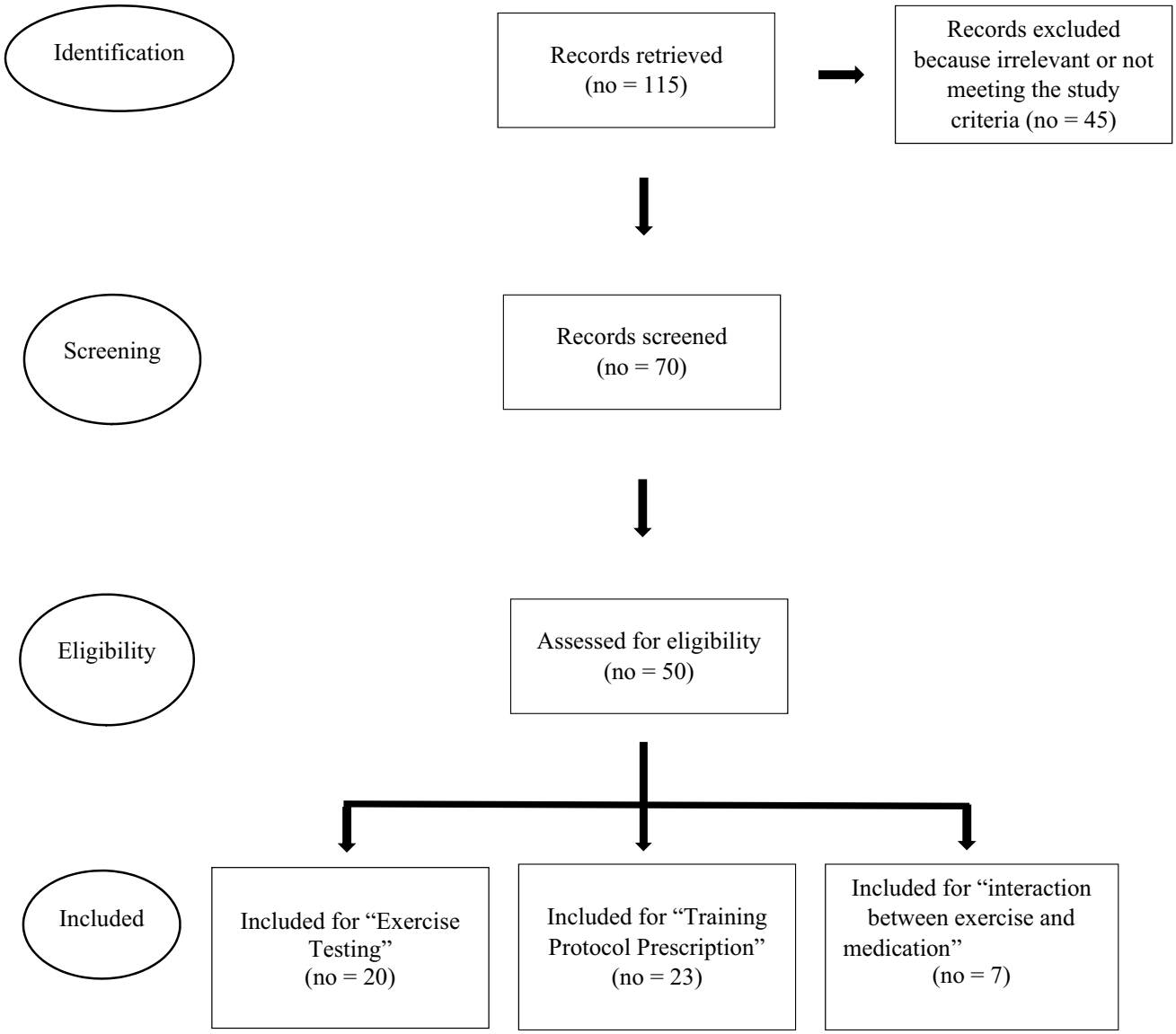

Fig. 1 Literature review flow chart: records retrieved, screened selected and included in the review

trial, one research report, five clinical studies; the remaining two included reviews that validated the results. Additionally, a book and a research article which both contain two published guidelines were used. The endurance assessment tests are summarized in Table 1. Table 2 presents the specifics of each test.

Balance assessment

Ten articles on balance, functional mobility, and postural instability testing were included as considered indexes that are helpful for a general evaluation of PD. One report tested patients with PD (H&Y stage 1–4) and provided a guideline that generally refers to each disease stage; the other studies did not specifically mention disease stage. Patients under medication were tested in four studies, in one the patients were in "off" status; in two they were "in-between"; six articles did not mention medication status. This rubric included one research report, three clinical studies; the remaining four were reviews that validated the results. Additionally, a book and a research article which both contain guidelines were used. Balance assessment tests are summarized in Table 3. Table 4 presents the specifics of each test.

Resistance assessment

Nine studies evaluated measurement tools for assessing muscular strength; there was one research report and 6 clinical studies. The American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription and the

Table 1 Endurance assessment tests

Author	Year	Design	Subject	H&Y disease stage	Medication status	Test
Light et al	1997	Clinical study	PD CG	4–5	On medication	2MWT 6MWT
Noonan et al	2000	Review	PD Other disease	Not reported	Not reported	Modified Bruce protocol on treadmill Astrand-Rhyming submaximal protocol on cycle ergometer
White et al	2009	RCT	PD	1–3	On medication	2MWT
Speelman et al	2012	Research report	PD CG	Not reported	On medication	Astrand-Rhyming submaximal protocol on cycle ergometer
Cancela et al	2012	Comparative study	PD	1–3	On medication	2MST 6MWT
Keus et al	2014	Guideline	PD	Not reported	Not reported	10MWT Borg scale
Bryant et al	2015	Clinical study	PD	2–3	Not reported	Modified Bruce protocol on treadmill
Bloem et al	2016	Review	PD	Not reported	Not reported	6MWT 1OMWT
Penko et al	2017	Clinical study	PD	1–3	On medication	GXT on cycle ergometer Borg scale
Mavrommati et al	2017	Cross sectional study	PD CG	Not reported	Off medication	GXT on cycle ergometer Borg scale
Riebe et al	2018	Guideline	PD	Any stage	On medication	10MWT 6MWT GXT on treadmill GXT on ergometer

PD Parkinson disease, *CG* control group, *GXT* graded exercise test, *RCT* randomized controlled trial, *2MWT* 2 min Walk Test, *6MWT* 6 min Walk Test, *2MST* 2 min Step Test, *10MWT* 10 min Walk Test

European Guidelines for Physiotherapy were examined for all disease stages. Six included PD patients with mild to moderate disease, generally in "on" status. Only one study involved older adults, without specifying the chronic conditions. All resistance assessment tests are summarized in Table 5. Table 6 presents the specifics for each test.

Flexibility assessment

One clinical study was reviewed for flexibility and range of motion (ROM) evaluation of mild to moderate disease. One book containing guidelines was used. Both works included PD patients in their "on" status. All flexibility assessment tests are summarized in Table 7. Table 8 presents the specifics of each test.

Training protocol prescription

The beneficial effects of exercise programs are marked in both healthy aging and PD [16]. There is also a strong connection between FITT of regular exercise and physical function in PD. Unfortunately, the optimal exercise type and dose are yet to be identified. There is much uncertainty about whether exercise influences the risk of developing the disease [17]. A better understanding of the mechanisms underpinning the exercise effect is important, as it will lead to more targeted interventions for optimal physical activity.

Since the current literature is scarce, the ACSM Guidelines for Exercise Testing and Prescription recommend improving of four main factors: gait, transfer, balance, and functional capacity. Major issues are the level of physical exertion which a PD patient can be subjected to and the most effective non-pharmacological modality (e.g., physiotherapy, walking, running, strength training or functional exercises) that can be safely prescribed. Recently, complementary programs like dance and Tai Chi have been positively re-evaluated [18]; such challenging exercises train multiple aspects of physical status simultaneously. For example, they improve walking speed, direction changes, and muscle strength in balance and gait. Furthermore, aerobic training and the "random practice" have beneficial effects of task-switching capability, particularly for PD patients. It is essential to prescribe a variety of activities to overcome the difficulties of PD patients to change activities and perform two actions simultaneously. Random practice and variation of movements will help to improve this.

Clinicians can adapt exercises from the training programs for healthy adults; indeed, both healthy adults and early-stage PD patients may present similar improvements in their general fitness and functional capacity [19]. The only advice is to adapt exercises to each person, taking into account

Table 2 Summary of endurance assessment tests

Test	Test Abbr	Goal	Description	Devices	Time	H&Y stage
2-min Walk Test	2MWT	Functional capacity, walking ability	Subjects walk as far as possible in 2 min. Rest breaks and assistive devices allowed	Stopwatch	2 min	1–4
6-min Walk Test	6MWT	Physical capacity and gait	Subjects cover as much ground as possible on a standardized walkway for 6 min. Assistive devices allowed; subjects can pause if necessary	Stopwatch, meter, chair, marker, 12-m hallway	< 10 min	1–4
Two-minute Step test	TMST	Aerobic capacity	Subjects begin stepping in place, raising the knee to the mark on the wall for 2 min. The number of times the knee reaches the right height is the score	Stopwatch, tape measure, marker	< 2 min	1–3
Modified Bruce protocol during Graded Exercise test		Cardiac functional capacity	Subjects walk on an horizontal treadmill in a graded exercise test with electrodes on the chest to monitor electrocardiogram. Every 3 min, treadmill speed, and incline are increased. During the few intervals only the slope increases. There are 7 stages	Treadmill, breathing devices, electrocardiogram devices, blood pressure cuff	Depends on subject's capacity	1–3
Åstrand-Rhyming protocol during Graded Exercise test		Maximal functional capacity	After 1 min of warm-up at 50Watt resistance, the workload increases during the first 3 min of the test. During the last 3 min, the workload is constant to achieve a steady-state heart rate. Subjects maintain a cycling rate of 70 revolutions per minute (rpm). If the heart rate in the last minutes differs by more than 5 beats per minute, the test is prolonged by 1 min. The exercise test is followed by a cooling-down period of 3 min	Stationary cycle ergometer	6 min	1–3
Borg Ratio Scale	RPE	Physical capacity	During the stress test, subjects indicate a value from 6 to 20 for personal perceived exertion every minute	6–20 rate scale	Depends on test duration	1–5

Table 3 Balance assessment tests

Author	Year	Design	Subject	H&Y stage	Medication status	Test
Noonan et al	2000	Review	PD Other diseases	Not reported	Not reported	TUG
Brusse et al	2005	Research report	PD	1–4	Not reported	FRT TUG BBS
Dibble et al	2006	Evaluation study	PD	Not reported	On medication	FRT BBS DGI TUG
Jacobs et al	2006	Comparative study	PD CG	Not reported	On-Between-Off medication	FRT RPT SLST
Mancini et al	2010	Review	PD Other disease	Not reported	Not reported	Tinetti test TUG SLST BESTest FRT
Keus et al	2014	Guideline	PD	Not reported	Not reported	BBS DGI TUG MiniBEST
Chomiak et al	2015	Cross-sectional study	PD	Not reported	On-between medication	SLST
Bloem et al	2016	Review	PD	Not reported	Not reported	Tinetti test BBS DGI Mini-BESTest TUG
Opara et al	2017	Review	PD	Not reported	Not reported	BBS TUG Tinetti test Mini BESTest
Riebe et al	2018	Guideline	PD	Any stage	On medication	FRT TUG RPT SLST

PD Parkinson disease, *CG* control group, *BBS* Berg Balance Scale, *TUG* timed up and go test, *BESTest* Balance Evaluation System Test, *DGI* Dynamic Gait Index, *RPT* Retropulsion Test, *SLST* One Leg Stance Test, *FRT* Functional Reach Test

cardiorespiratory functions, physical limitations, mental health, and disease stage progression assessed during a previous medical visit [11]. Differently, in stage 4 PD, patients need modified exercises because of the severe limitations in balance and gait. Contrarily, in bedridden patients in stage 5, the program is restricted to a palliative approach to prevent deformities or rapid physical decline [20]. Figure 2 illustrates the main objectives at each stage of PD.

Endurance training

In this section, 19 articles were included; the endurance training interventions are summarized in Table 4. The most recent papers were published in 2019, the oldest one dates from 2000. Seven studies were randomized controlled trials, six reviews, four works containing guidelines for PD management; among the remaining two, one was a clinical trial and the other a test–retest reliability study. All the studies reported benefits and improvements in PD patients after following a program of aerobic therapy that included a minimum of 20 min and a maximum of 60 min of activity. The outcome scores and main features of the studies are summarized in Table 9.

Resistance training

Twelve studies were included; the resistance training interventions are summarized in Table 5. The most recent articles were published in 2019, the oldest one dates from 2003. Two were randomized controlled trials, six reviews, four works include guidelines for PD management; of the remaining two, one was a clinical trial and the other a test–retest reliability study. All the studies reported benefits and improvements in PD patients after following a program of resistance

Table 4 Summary of balance assessment tests

Test	Test Abbr	Goal	Description	Devices	Time (min)	H&Y stage
Timed Up and Go Test	TUG	Functional mobility	Subjects get up from a chair, walk 3 m at a comfortable and safe pace, turn and walk back to sit down on the chair. The use of assistive devices is allowed	Chair, stopwatch, 3-m walkway	< 5	1–3
Tinetti Balance and Gait Test		Static and dynamic balance	Subjects sit on a chair, rise, stay standing, turn 360° and then sit back down. Next, they walk a few meters at a normal speed, turn, and walk back at a "fast but safe" speed, then sit back down. Pay attention to the length and height of the steps, the symmetry and continuity of the steps and straightness of the trunk. The use of assistive devices is allowed	Armless chair, stopwatch, 3-m walkway	10–15	1–4
Retropulsion Test	RPT	Postural stability	Subjects stand with eyes open and feet slightly apart. The test measures the response to sudden, strong posterior displacement produced by a pull-on shoulders. More than 2 steps backward mean abnormal balance	None	1	1–4
One-leg Stance Test	SLST	Static balance	Subjects with eyes open are asked to stand on either their left or right leg and are instructed to keep their legs from touching and to maintain single-leg stance for as long as possible. The test and time begin once the foot is lifted off the floor and ends when placing the lifted foot on the floor or with arm movements and the placing of their hand on a chair that was positioned beside them for support if needed. Each leg is tested three times unless subjects perform perfectly on the first two trials	Stopwatch	1	1–4

Table 4 (continued)

Test	Test Abbr	Goal	Description	Devices	Time (min)	H&Y stage
Åstrand-Rhyming protocol during Graded Exercise Test	FRT	Dynamic balance	Subjects stand, make a fist and forward flex the dominant arm without touching the wall with their arm. Taking note of the starting position at the 3rd metacarpal head on the yardstick. Subjects reach as far forward as possible without taking a step. Various reaching strategies can be used. Take note of the end position and compare the distance between the start and end point	Wall, yard stick, ruler	5	1–4
Balance Evaluation System Test	BESTest	Balance systems	Subjects have shoes off and perform 36 tasks, each 0–3 scored and grouped into six systems: biomechanical constraints, stability limits/verticality, anticipatory postural adjustments, postural responses, sensory orientation and stability in gait. The use of assistive devices corresponds to lower score	Wall and floor tape, inclined ramp, stair step, obstacles, free weight, chair, stopwatch	20–30	1–4
Mini Balance Evaluation Systems Test	Mini-BESTest	Dynamic balance	Subjects have shoes off and perform 14 items, each 0–2 scored and grouped into four systems: anticipatory postural adjustments, reactive postural control, sensory orientation, postural responses, sensory orientation, dynamic gait. The use of assistive devices corresponds to lower score	Wall and floor tape, inclined ramp, stair step, obstacles, free weight, chair, stopwatch	10–15	1–4
Berg Balance Scale	BBS	Static and dynamic balance	Subjects are tested during predetermined tasks grouped in 14 items, each 0–4 scored to travel as far as possible in 2 min. Rest breaks and assistive devices are allowed	Stopwatch, ruler, 2 chairs, step, 15 m walkway	15–20	2–3

Table 5 Resistance assessment tests

Author	Year	Design	Subject	H&Y stage	Medication status	Test
Koller	1986	Clinical study	PD CG	1–2	Not reported	MMT HGT
Durmus et al	2010	Clinical study	PD CG	2–3	On medication	Isokinetic dynamometer
Buckley et al	2012		PD	1–3	On medication	1-RM
Cancela et al	2012	Comparative study	PD	1–3	On medication	ACT 30SCST
Keus et al	2014	Guideline	PD	Not reported	Not reported	FTSTS
Frazzitta et al	2015	Clinical study	PD CG	3	On medication	Isokinetic dynamometer
Lombara	2017	Review	PD	Not reported	On medication Off medication	MMT ACT CST Isokinetic dynamometer
Riebe et al	2018	Guideline	PD	Any stage	On medication	MMT ACT Isokinetic dynamometer
Clael et al	2018	Research report	PD	1–4	On medication	Isokinetic dynamometer

PD Parkinson disease, *CG* control group, *MMT* Manual Muscle Test, *HGT* Handgrip Test, *1-RM* one Repetition Maximum, *ACT* Arm Curl Test, *30SCST* 30 s Sit to Stand Test, *FTSTS* Five Time Sit to Stand Test

physical therapy (minimum of 1–4 sets and multiple repetitions) in those with mild-to-moderate disease. Results and specifics of the studies are summarized in Table 10.

Flexibility training

None of the eight studies that analysed flexibility reported which is the best program for each H&Y stage. The studies included patients with early to moderate stage but none with more advanced stages. The most recent article was published in 2018 and the oldest in 2008. Three were randomized controlled trials, one was a review, four works contain guidelines for PD management. Only general recommendations about exercise frequency, time, and intensity were mentioned. Considering the exercise type, the patients were encouraged to follow a complete flexibility training program that mobilizes each body district, without distinction. The results and main features of the studies are summarized in Table 11.

Interaction between exercise and medication

Seven studies were reviewed that summarized current knowledge about the effects of physical exercise on drug absorption and efficacy in PD. Six specifically tested the effects of aerobic exercise on L-DOPA administration in PD patients with H&Y stage 1–3; no study tested patients with more advanced stage and no articles were found on drug response to resistance and flexibility exercises; only one exploited a MPTP-toxin parkinsonian mouse model used by two other studies about molecular mechanisms underlying the beneficial effects of physical exercise. One review article was added as support.

In three studies, patients exercised on a treadmill and on a cycle ergometer in four. As final assessment tools, blood samples were taken in three studies to monitor drug concentrations, UPDRS-III score was used in three, whereas only one trial reported physiological parameters (heart rate, blood pressure). The animal-based study also used behavioral testing, immunohistochemistry, and transcriptome analysis. Outcome scores and main features of the studies are summarized in Table 12.

Discussion

Endurance and balance assessment

There are valid strategies for performing endurance assessment; the choice will be dictated primarily by the focus of the study. During a clinical exercise test for endurance, also known as a fitness assessment, subjects are generally in their "on" status and are monitored while doing a battery of exercises at maximal or submaximal intensity depending on disease severity [21], graded workload exercises (GXT) on a treadmill or a stationary cycle ergometer until exhaustion [19, 22]. Likewise, patients can be tested with constant workload or free body exercise utilizing step tests. Aerobic fitness, an important parameter for most sports, can be severely impaired in illness, worsening the patient's quality

Table 6 Summary of resistance assessment test

Test	Test Abbr	Goal	Description	Devices	Time	H&Y stage
Handgrip Strength Test	HST	Upper limb strength	When ready, subjects squeeze the dynamometer with maximum isometric effort, which is maintained for about 5 s	Handgrip dynamometer	5 s	1–3
Isokinetic Strength Test		Upper/lower limb strength	Subjects are positioned so that the body movement to be measured is isolated. The equipment is set at different speeds and the force applied can be measured throughout the range of movement. The results are often reported at different speeds; comparison of the relative strengths of the different sides of the body can show specific muscular limitations	Isokinetic testing equipment	5 s	1–3
Manual Muscle Test	MMT	Individual or grouped muscle strength	Subjects are instructed to hold the corresponding limb or appropriate body part to be tested at the end of its available range while the practitioner provides opposing manual resistance. Manual resistance and length of the weight arm can be increased or decreased. It is scored 0–5, 0 means patient does not move, 5 means complete range of motion and ability to withstand pressure	None or myometer	< 1 min	1–4
Arm Curl Test	ACT	Upper limb strength	Subjects sit down on a chair and do as many arm curls as possible in 30 s	Stopwatch	30 s	1–3
Chair Stand Test	CST	Lower limb strength	Subjects sit on a chair with arms crossed over the chest. They are asked to stand up as quickly as possible safely without using arms. Timing begins on the word "Go" and stops when the subject comes to the last complete stand or sits after the last stand	Stopwatch, chair	5 min	1–3
Five Time Sit to Stand Test	FTSTS	Lower limb strength	Subjects stand up and sit down 5 times as quickly as they can. Previous training is allowed. A time test greater ≥ 10 s indicates a higher risk of disability and falling	Chair, stopwatch	2 min	1–4

Table 6 (continued)

Test	Test Abbr	Goal	Description	Devices	Time	H&Y stage
One Repetition Maximum Test	1-RM	Maximum lower or upper limb isotonic strength	After a warm-up, subjects choose a weight that is achievable. Then after a rest of at least several minutes, the weight is increased and tried again. Subsequent weights are increased until the subject can only repeat one full and correct lift of that weight. The maximum weight lifted, and the sequence of lifts should be recorded as these can be used in subsequent tests to help following assessments	Free weights, stopwatch	Depends on the number of series	1–3

of life. The patient's overall health and physical status can be evaluated to obtain the baseline measurements for programming a personalized exercise regimen.

Clinicians should exploit several different screening tools to determine baseline parameters [e.g., height, weight, resting heart rate (RHR), and resting blood pressure (RBP)] and compare them to the measurement taken during peak exercise or after the test. Another main objective of these tests is to measure cardiovascular performance, metabolic parameters (e.g., maximal oxygen uptake [VO_2max], METs) via stress testing and monitor the cardiopulmonary response to oxygen supply, rate of perceived exertion (RPE) [23], and electrocardiogram (ECG) continuously monitored during activity. Moreover, test results may be helpful to determine functional problems, to predict the risk of falls [69], and to evaluate the effectiveness of an intervention [24]. Attention should be directed to testing balance, falling [25], and gait [26] using, for example, the Timed Up and Go (TUG), the Åstrand-Rhyming protocol during GXT, and the Berg Balance Scale (BBS), which are the most widely used evaluation tools [11, 27–29].

Common endurance tests, such as the 6-min walk test [27, 28] or the 2-min walk test [30] for patients with advanced PD [31], can be easily administered without special equipment and provide a complete framework of aerobic and gait capacities when coupled with GXT protocols. Because PD is a progressive disease, patients require repeated physical evaluations over time and adjustments to their training program according to disease stage [11], motor disabilities, and L-DOPA-induced complications, which may preclude safe adherence to an endurance exercise protocol (Tables 13–15). The following indications are recommended for all patients with PD (1–5 H&Y):

- PD patients often suffer from cardiac dysrhythmias.
- Exercise should start 45–60 min after medication has been taken.
- Inquire about changes in medication.
- Patients with significant fluctuation should be tested while in the "on" and the "off" status.
- Individuals unable to perform a GXT (due to risk of falling, severe stooped posture, deconditioning) may require a radionuclide stress test or stress echocardiography.
- Continuously monitor heart rate, blood pressure, ECG, RPE, and other signs.
- Standard procedures, contraindications, recommended monitoring intervals, and standard termination criteria are used in exercise testing of individuals with PD.
- For deconditioned patients with lower limb weakness, compromised balance or history of falling, precautions should be taken (gait belt, harness, and technician assistance), especially at the final stages of the test when fatigue occurs, and the individual's walking may worsen.

Table 7 Flexibility assessment tests

Author	Year	Design	Subject	H&Y stage	Medication status	Test
Cancela et al	2012	Comparative study	PD	1–3	On medication	Back scratch Sit and Reach test
Riebe et al	2018	Guideline	PD	Any stage	On medication	Back scratch Sit and Reach test Goniometer Flexometer Inclinometer

PD Parkinson disease

- Deep brain stimulation device, if present, should be deactivated to avoid interference with ECG recording. Remember that, without stimulation, the patient will be in a compromised mobile state and will not be able to achieve maximal tolerance (physical discomfort, tremor, cramping, and emotional symptoms).

Resistance assessment

Muscle weakness is a primary symptom of PD, not only due to consequences of aging and inactivity. It is directly correlated with lesion of the basal ganglia that impedes activation of motor neurons and results in muscle weakness [32]. Strength can be tested by measuring the maximal amount of force a muscle group can exert at one time. The primary goal is to train and improve muscle strength by developing a personalized program after baseline assessment. The exercise tests are definite for each muscle group with instrumental measurements using tensiometers or dynamometers [33–35]. Upper body exercise tests include the Static Handgrip Strength Test [36], the Manual Muscle Test [11, 36, 37], and the Arm Curl Test [11, 37, 38], while for the lower body the Chair Rise Test [37] or the Five Time Sit to Stand Test [29] are recommended. Note that the One-Repetition Maximum (1-RM) test is not limited to only one exercise type and that it can be conducted in a wide variety of assessments [39] (Tables 13, 14, 15). The following indications are recommended for all patients with PD (1–5 H&Y):

- The standard index for strength assessment is the 1-RM, which is determined after completing a series of submaximal repetitions of a specific exercise.
- Resistance is initially within the patient's perceived capacity (50–70% of capacity). Only when the series is completed correctly it can be progressively increased.
- It may be necessary to use very light weights or substitute them with household items.
- A metronome is a useful to measure how long the patient can keep up with the rhythm.
- A warm-up phase of 5–10 min is always recommended.
- Patients at risk for cardiovascular, pulmonary or metabolic diseases should perform adapted tests.

Flexibility assessment

Flexibility refers to the ability to completely move a joint during sports and daily activities. Continuous training to exercise joints is important in injury prevention. At the early stages of the disease, patients often experience rigidity of limbs, neck or trunk, hip and shoulder, which leads to a reduced ROM, postural imbalance [10] and instability. Because of the increased resistance to movement, patients exhibit bradykinesia, muscle stiffness, pain, and cramps, fixed facial expression, difficulty turning over in bed or getting out of a chair and performing activities of daily living [29].

Since the entire body is often involved, diverse tests are administered to assess the level of flexibility and then tailor the best exercise battery to the patient's needs.

Exploited devices in assessment include goniometers, electrogoniometers, tape measures, inclinometers, and Leighton flexometer [38]. While, for visual measurement of ROM, flexibility level can be estimated directly by screening the neck, trunk, hip, shoulder and postural motion observation through simple flexion, abduction, adduction, rotation, supination, pronation, and inversion recorded in degrees [11] (Tables 13, 14, 15). The following indications are recommended for all patients with PD (1–5 H&Y):

- Have the patient warm-up before the evaluation and use adapted protocols as needed.
- Show the patient how to perform the movement being evaluated.
- Encourage the patient to stretch to the point of slight discomfort without pain.
- Perform all tests during peak medication when the patient's mobility is optimal.

Table 8 Summary of flexibility assessment tests

Test	Test Abbr	Goal	Description	Advantage	Disadvantage
Goniometer		General Joint flexibility	The center of the goniometer is placed at the axis of rotation of a joint, and the arms of the goniometer are aligned with the long axis of the bones of the adjacent segments or to an external reference		Difficulty in maintaining the position of the arms of the goniometer along the bones of the segments throughout the measurement, and the axis of rotation is not always clear, especially for complex joints
Inclinometer		Angles of slope measurement (gravity-dependent goniometer)	The therapist holds the instrument on the patient, who begins in a standard starting position. The therapist zeroes-out the inclinometer and then instructs the patient to bend the joint through its range of motion (ROM). The inclinometer's final reading is the ROM measurement	Easier to use with greater accuracy	
Leighton flexometer		Joint flexibility (neck, trunk, shoulder, elbow, radioulnar, wrist, hip, knee, and ankle joints)	The flexometer is strapped to the body segment to be measured. Lock the dial at 0 degrees at one extreme of the ROM. After the body segment has moved to the new position, lock the pointer at the other extreme of the range. The degree of arc through which the movement takes place is read directly from the dial	No need to identify the axis of rotation	
Sit and Reach Test	SRT	Lower back and hamstring muscles tightness	The subject is sitting on the floor with legs stretched out straight ahead, without shoes. Feet are placed flat against the box. Both knees should be locked and pressed flat to the floor. With the palms facing downwards, and the hands on top of each other or side by side, the subject reaches forward along the measuring line as far as possible. After some practice, the subject reaches out and holds that position while the distance is recorded	Easy and quick to perform with sit and reach box, if using the standard testing procedure	Variations in arm, leg and trunk length can make comparisons between individuals misleading. This test is specific for ROM muscles and joints of the lower back and hamstrings, not for other parts of the body

Table 8 (continued)

Test	Test Abbr	Goal	Description	Advantage	Disadvantage
Back Scratch Test	BST	Shoulder range of motion	After a warm-up phase, subjects stand while they touch the fingertips together behind the back by reaching over the shoulder and under the elbow. If the fingertips touch, the score is zero. If they do not touch, measure with a ruler the distance between the fingertips (a negative score); if they overlap, measure by how much (a positive score). Test termination is recommended if the subject experiences pain	The test can be repeated every several weeks to determine what progress patient has made	

Endurance training

Endurance exercise training refers to exercise that improves cardiorespiratory fitness, i.e., VO_2max, and cardiorespiratory endurance that refers to how long an individual can perform an activity using large muscle groups. It has been suggested that PD patients can benefit from aerobic training and maintain high levels of physical function [40, 70] by performing high intensity exercises. Alternatively, leg cycle ergometry, arm ergometry or combined ergometry are valid strategies to record physical performance or cardiorespiratory fitness [41–44] in patients with severe limitations [11]. Exercise training may involve repetitive movements that guide and gradually activate the neuromuscular system by working on motor functions over time. Furthermore, good results can be obtained with a gradual aerobic exercise program for cardiovascular autonomic regulation by improving systolic blood pressure and response to orthostatic stress [19, 45]. Moreover, improvements in general fitness [20, 43, 46], fatigue, bradykinesia, gait [47–49], and ADL [50] are obtained after exercise at light-moderate intensity in patients with mild-to-moderate PD.

Animal studies have associated exercise dose (e.g., frequency, duration, intensity, and type of exercise) to neuroprotective effects [51]. Differently in humans, benefits of endurance exercise have been observed only in general motion, walking speed, balance improvement, and cortical reorganization favored by neuroplasticity events [52–54]. Furthermore, aerobic exercise has been proved to be effective for improving heart, lungs, metabolic, and circulatory systems by reducing the risk of chronic diseases such as diabetes, heart diseases, and stroke.

However, the evidence for optimal exercise dose treatment to improve function in PD remains unknown. While it is recognized that all approaches lead to positive effects, the choice of the protocol best tailored to each patient must, firstly, guarantee safety during execution. Clinicians need to consider the stage of the illness, drug-dependent status, and physical limitations, while encouraging engagement in light, moderate or vigorous exercise, according to maximum capability and motivation also in deconditioned PD patients (Tables 13, 14, 15).

Resistance training

In almost all PD patients, muscle strength declines most notably in the flexors and extensors of the hip, knee, wrist, hands, and core muscles [49]. This reduction compromises gait and general physical functions, increasing the risk of falls. Muscle weakness is a serious impairment that alters the individual's ability to perform activities of daily living such as simply standing up from a chair or stepping. A valid approach is to prescribe specific training protocols

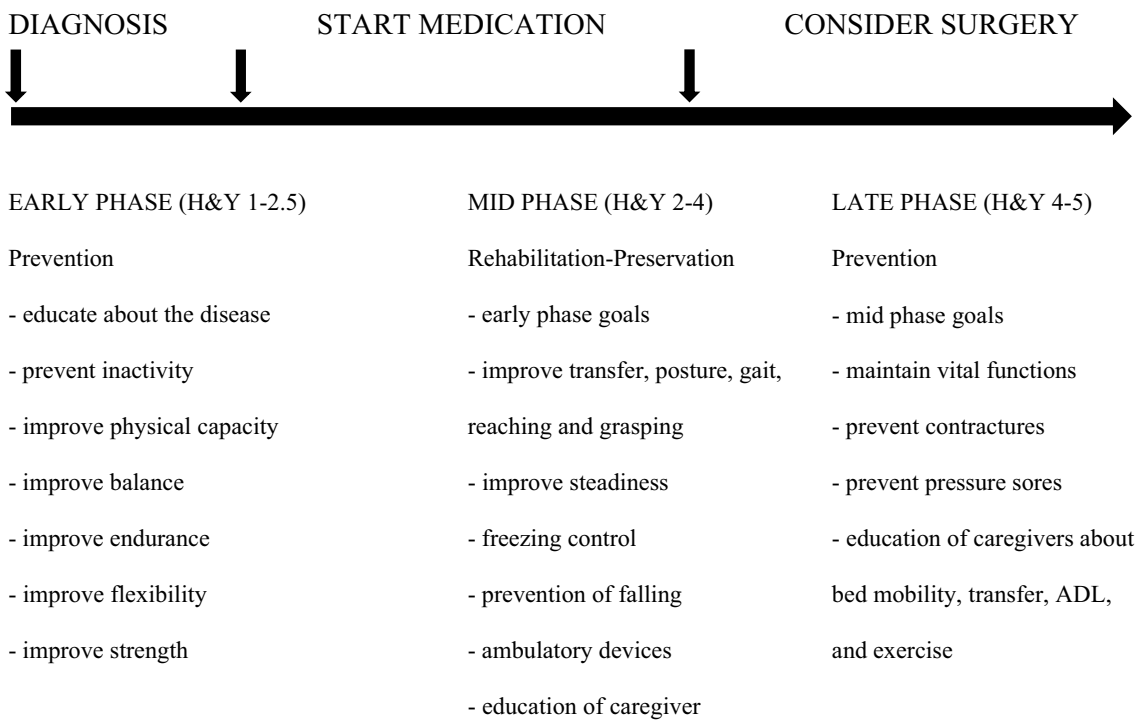

Fig. 2 Main objectives at each PD stage

that exercise major muscle groups, especially the lower limbs, without causing excessive fatigue [55–57]. Resistance training can comprise a variety of exercises, use of weight machines or bodyweight; generally, 2–3 days of weekly resistance exercise at moderate to high intensity with more than 1 set and multiple repetitions are recommended. Although the studies reviewed here focused on early and moderate stages (H&Y stage 1–3) of PD, the appropriate exercise type depends on the individual fitness, stage of illness and experience with physical activity (Tables 13–15).

Flexibility training

Rigidity is an obstacle to movement, especially when it affects lower limbs resulting in shorter steps and altered walking pace. All studies agree that regular stretching is essential in PD exercise programs. When performed multiple times per week or daily in adjunct with mobility and resistance exercises [15, 17], it may diminish muscle rigidity accompanying the illness [58]. Exercise also ameliorates muscles and joints flexibility and general health status [11, 53]. To facilitate routine movements, few tips are necessary to bring significant benefits, such as adapting both exercise and stretching time to comorbidities and PD limitations, not dynamic movements and avoiding pain. Information on the exact duration of stretching therapy is unknown. One study found a loss of efficacy 2 months after the end of the therapy and recommended continuation and repetition of flexibility training over time, especially near the peak effect of L-DOPA [59], to maintain benefits (Tables 13, 14, 15).

Interaction between exercise and medication

Physical activity in patients with PD shows improvements in motor symptoms, but, more importantly, also in non-motor signs, since exercise involves many different brain areas. Pharmacotherapy for motor signs is helpful but may worsen non-motor symptoms, especially in the long term, or accentuate compulsive disorders. The duration of "on" periods and drug effectiveness diminish with chronic L-DOPA usage, probably due to disease progression rather than the treatment itself [60]. However, treatment interruptions to avoid adverse effects can lead to regression of the disease. To date, no studies have evaluated the impact of physical activity without pharmacological support, given the ethical restrictions on standards of care. Nevertheless, important discoveries concern the positive effects of physical activity on drug-induced disorders, such as amantadine or L-DOPA, still considered the gold standard therapy. Although some studies did not report significant gaps in L-DOPA metabolism, a different outcome during cycling exercise and at rest indicated [61–63] three different responses, as exercise can either increase or decrease L-DOPA absorption or induce no significant change (H&Y stage 2–3).

In individuals with idiopathic PD (H&Y stage 1–2.5), the UPDRS motor score, together with blood sample analysis

Table 9 Endurance training protocol

Author	Year	Design	Subject	H&Y stage	Frequency	Intensity	Time	Type	Other exercise	Results
Miyai et al	2000	RCT	PD-BWSTT + PT PD– PT + BWSTT	2.5–3	3 days/ week for 4 weeks	Speed at 0.5–3.0 km/h	45 min	BWSTT and PT	ROM-balance-gait exercise Occupational therapy	↑ ADL, motor performance, ambulation with BWSTT
Fisher et al	2008	RCT	PD-high ex PD-low ex PD-zero ex	1–2	24 sessions over 8 weeks	PD-high ex: > 3 METS 75% HRmax PD-low ex: ≤ 3 METS 50% HRmax	Max 45 min	BWSTT PT	Stretching Balance-gait exercise Resistance	↑ corticomotor excitability with high ex BWSTT
Gallo et al	2011	Guideline	PD	1–3	≥ 3 days/week ≥ 5 days/week ≥ 3 to 5 days/ week	Vigorous: ≥ 60% HRR Moderate: 40–60% HRR Light: < 40% HRR Forced: ≥ 30% of usual walking speed	30–60 min 20–60 min < 20 min Multiple sessions of ≥ 10 min	Weight-bearing Lower body ergometer	Neuromotor Flexibility Resistance	↑ CRF ↑ VO_2max
Cianci et al	2012	Guideline	PD	Not reported	5 days/week	Moderate high to high: 50–85% HR_{max}	30 min	Walking, jogging, running, swimming, dancing, chair aerobics, biking	Stretching Balance-gait exercise Resistance	↑ mobility and general health
Salgado et al	2013	Review	PD	1–3	Every other day	Moderate to High	30 min	Treadmill Cycling	Resistance and balance	↑gait ↑ ambulation ↑ bradykinesia
Shulman et al	2013	RCT	PD-low intensity PD-high intensity PD-stretching + resistance	1–3	36 sessions, 3 days/week for 3 months	Lower: increasing duration up to 40–50% HRR Higher: increasing duration, intensity, incline up to 70–80% HRR	max 50 min max 30 min	Treadmill	Stretching Resistance	↑ CRF ↑ gait speed
Frazzitta et al	2014	RCT	PD PD-CG	1–1.5	5 days/week for 4 weeks	Heart rate ≤ 60% Speed increases every 3 days by 0.05 stride cycles/s until a max of 3.5 km/h	3 h/day	Treadmill	Stretching Balance-gait exercise Occupational therapy	↑ BDNF and motor performance

Table 9 (continued)

Author	Year	Design	Subject	H&Y stage	Frequency	Intensity	Time	Type	Other exercise	Results
McGraw et al	2014	Review	PD	1–3	4–5 d · week	Regular	20–30 min	Treadmill Swimming Stationary bike	Resistance and functional training	↑gait speed ↑ stride length ↑ walking distance
Nadeau et al	2014	RCT	PD-mixed TT PD-speed TT PD-CG	1.5–2	1-h supervised session/week for 24 weeks 1-h home session/week for 24 weeks	Speed: 80%, 90%, 100% of preferential walking speed, later increased by 0.2 $km \cdot h^{-1}$	45 min	Treadmill	Flexibility	↑ motor non-motor signs ↑ endurance, speed, gait, life quality
Zoladz et al	2014	Clinical trial	PD	1–3	3 1-h sessions/week for 8 weeks	Moderate: 8 sets of 5 min interval exercise with 3 min at 80–90 rpm and 2 min at < 60 RPM 60–75% of HR_{max}	40 min	Cycle stationary ergometer	None	↑ BDNF ↑health status ↑inflammation
Ellis et al	2016	Guideline	PD	Not reported	2.5 h total/week	Moderate: 13 on 6–20 RPE scale	Not reported	Brisk walking Biking Jogging Swimming	Exercise with music, metronome	↑ walking speed-quality
Nelson et al	2017	Test–retest reliability	PD	1–3	1–2 times/week for at least 6 months	From moderate to moderately hard intensity up to 4–6 on 1–10 RPE scale	20 min session	Forward and Backward treadmill	None	Good TRR Positive HR-CRF range
Schenkman et al	2017	RCT	PD-high ex PD-moderate ex PD-CG	1–2	4 days/week for 6 months	High: 80–85% HR_{max} Moderate: 60–65% HR_{max}	30 min	Treadmill	None	Feasibility and safety of high intensity training
Oliveira de Carvalho et al	2018	Review	PD	1–3	3–5 days/week	Light: < 40% HRR Moderate: 40–60% HRR Hard: > 60% HRR	20–60 min	Walking Cycling	Resistance, flexibility and balance	↑ general benefit
Ahlskog et al	2018	Review	PD	1–5	Long term	Not specified	Not specified	Aerobic-type exercises	Resistance	↑ CRF ↑ activation-cognition ↑ BDNF ↑ brain volumes-connectivity

Table 9 (continued)

Author	Year	Design	Subject	H&Y stage	Frequency	Intensity	Time	Type	Other exercise	Results
Riebe et al	2016	Guideline	PD	1–3	3 days/week	Moderate: 40–59% HRR and 12–13 on 6–20 RPE scale	30 min	Walking Swimming Cycling Dancing	Resistance and flexibility	↑PD progression
Steiger et al	2019	Review	PD	1–3	2 sessions/week	70–80% HR_{max} > speed, incline, intensity, duration gradually	30–60 min	Treadmill Walking Cycle ergometer	Resistance and balance	↑ motor non-motor signs
Kim et al	2019	Review	PD	1–3	3–5 days/week	Moderate 13 on the 6–20 RPE scale	20–60 min	Ergometry Walking Aquatics	None	↑ general benefit

PD Parkinson disease, *CG* control group, *L-DOPA* Levodopa, *RCT* randomized controlled trial, *BWSTT* body weight supported treadmill training, *PT* physical therapy, *UPDRS* Unified Parkinson Disease Rating Scale, *TT* treadmill training, VO_2max maximal volume of oxygen consumption, *ADL* activity of daily living, *ROM* range of motion, *METS* metabolic equivalents, *RPE* rate of perceived exertion, HR_{max} maximum heart rate, *BDNF* brain-derived neurotrophic factor, *HRR* heart rate reserve, *TRR* test retest reliability, *CRF* cardiorespiratory fitness

[64], during endurance exercise on a bike ergometer showed a slight improvement in motor response to L-DOPA administration when compared to resting condition under medication. Likely higher blood pressure and heart rate due to exercise contribute toward better drug transport over the blood–brain barrier and reduced drug storage in the periphery. More recently, these physiological parameters were studied together with the endocrine release of norepinephrine [65] during on and off medication status, at rest, and during a treadmill stress test. The results confirmed a lower autonomic response in the PD groups compared to the healthy controls. Indeed, while much work remains to be done, it was hypothesized that antiparkinsonian medication does not affect autonomic responses or motor outcomes; in contrast, abnormalities in heart rate or blood pressure are predominantly due to the disease. In a few conflicting cases [66] it was reported that L-DOPA and dopamine agonists may have had a negative effect on systolic blood pressure during a treadmill protocol, leading to limited cardiopulmonary responses to exercise in the PD patients under medication.

Physical and pharmacological therapies appear to act on the same molecular pathways but lead to opposite effects. Apparently both regulate dopamine and neuropeptides levels [52] but L-DOPA increases the release of neurotransmitters and interrupts the regular signaling between receptors and substrates, while physical exercise tends to rebalance dopamine levels and the body's homeostasis by mobilizing gene profiling and facilitating brain plasticity processes [67].

Other experiments conducted on MPTP-treated mice [68] identified three genes that normally regulate cell growth and neurogrowth factors, which in PD are activated by exercise and inhibited by drugs. Despite this general trend, the CREB1, RICTOR, and L-DOPA genes also respond slightly differently, depending on the cortical area in which they are expressed and on the disease stage. This difference may explain the diverse outcomes in patients during therapy and the choice to defer or limit drug dosage in those whose life quality is not seriously affected by PD. Although other data are needed to determine quantitatively and qualitatively how physical activity interacts with drugs, it is established that their combination is more beneficial than single treatment alone.

Limitations

This review has some limitations. Many of the studies were of short duration and involved a small sample of patients without a control group. Most had mild to moderate disease; few studies included patients at more advanced PD stages. Since PD is a chronic degenerative disorder, studies of longer duration and with larger populations are needed

Table 10 Resistance training protocol

Author	Year	Design	Subject	H&Y stage	Frequency	Intensity	Time	Type	Other exercise	Results
Hirsch et al	2003	RCT	PD	Not reported	3 times/week for 10 weeks	60% 4-RM 80% 4-RM	1 set, 12 repetitions 15 min	Weights machine	Balance	↑ muscle strength ↑ fatigue-discomfort
Gallo et al	2011	Guideline	PD	1–3	2–3 days/week	Moderate to hard: 60–80% 1-RM for beginners-intermediate Very light: 40–50% 1-RM for older	2–4 sets, 8–15 repetitions 1 set for beginners	Major muscle group and multiple joints	Aerobic Flexibility Neuromotor	↑ muscle strength ↑ power
Cianci et al	2012	Guideline	PD	Any stage	2–3 days/week	Stop if pain Smooth movements	1 set, 10–15 repetitions	Standing, seated, on the ground with machines or own body weight	Aerobic, strength, boxing, dance, yoga, tai chi, pilates	↑ functional ability
Salgado et al	2013	Review	PD	1–3	2–3 days/week	High load resistance	3 sets	Concentric and eccentric contractions	Aerobic Balance	↑gait ↑ ambulation ↑ bradykinesia
Shulman et al	2013	RCT	PD-stretching + resistance PD-low intensity PD-high intensity	1–3	36 sessions, 3 days/week for 3 months	Increased weight as tolerated	2 sets, 10 repetitions on each leg	Leg press Leg extension Leg curl	Stretching Aerobic	↑ CRF ↑ gait ↑ fitness ↑ muscle strength
McGraw et al	2014	Review	PD	1–3	Not reported	Regular	Not reported	Free weights exercise for major muscle groups	Aerobic and functional training	↑gait speed ↑ stride length ↑ walking distance
Uhrbrand et al	2015	Review	PD	1–2	1–3 sessions/week for 4–104 weeks	40–80% 1-RM	1–3 sets, 5–20 repetitions	Lower and upper extremities with machines	Aerobic	↑muscle strength ↑walking performance ↑UPDRS III
Ellis et al	2016	Guideline	PD	Not reported	2–3 days/week	Start slowly and increase repetitions gradually	2 sets, 8–12 repetitions	Squat, Bridge, Hip rotation, Trunk stabilization, Push-up, Heel raise	Endurance Flexibility Balance	↑ muscle strength ↑ balance ↑ walking ↑ mobility
Riebe et al	2018	Guideline	PD	1–3	2–3 days/week	40–50% 1-RM for beginners 60–70% 1-RM for advanced exercisers	≥ 1 set, 8–12 repetitions or 10–15 repetitions for beginners	Avoid free weights Use of weight machines and resistance devices	Aerobic Flexibility	↑PD progression

Table 10 (continued)

Author	Year	Design	Subject	H&Y stage	Frequency	Intensity	Time	Type	Other exercise	Results
Oliveira de Carvalho et al	2018	Review	PD	1–3	2–3 sessions/week	Light: 40–50% 1-RM Moderate: 60–80% 1-RM Hard: > 80% 1-RM	2–4 sets, 8–15 repetitions	Large muscle groups	Aerobic Flexibility Balance	↑ motor signs ↑ brain plasticity
Kim et al	2019	Review	PD	1–3	2–3 days/week	40–50% up to 60–80% 1-RM; 2–4 min recovery in between sets and muscle groups	1–3 sets, 8–12 repetitions	Free weights Weight machines Elastic bands for major muscle groups	Aerobic	↑ general benefit
Steiger et al	2019	Review	PD	1–3	2 times/week	To the point where any more repetition can be performed, increase weight or repetitions if necessary	2–3 sets, 10–15 repetitions	Major muscle groups	Endurance Balance Tai chi	↑ muscle strength ↑ mobility ↑ UPDRS III

PD Parkinson disease, *CG* control group, *L-DOPA* Levodopa, *RCT* randomized controlled trial, *UPDRS III* Unified Parkinson Disease Rating Scale III, *1-RM* One Repetition Maximum

Table 11 Flexibility training protocol

Author	Year	Design	Subject	H&Y disease stage	Frequency	Intensity	Time	Type	Other exercise	Results
Fisher et al	2008	RCT	PD-high ex PD-low ex PD-zero ex	1–2	24 sessions over 8 weeks	Not reported	45 min · session	Passive and active ROM	Balance, gait, resistance, functional, treadmill	↑ corticomotor excitability
Gallo et al	2011	Guideline	PD	1–3	2–3 days/week Daily	30–75% of MVC	60 s for each exercise	Major muscle units stretches, trunk and spine stretches, static and dynamic stretches	Endurance, resistance, neuromotor exercise	↑ general health
Cianci et al	2012	Guideline	PD	Not reported	3–4 repetitions for each stretch 3–4 times/week or daily	Do not bounce, do not stretch to the point of pain	10–30 s	Standing, lying and seated stretches	Aerobic, strength, boxing, dance, yoga, tai chi, pilates	↑ flexibility
Shulman et al	2013	RCT	PD-stretching + resistance PD-low intensity PD-high intensity	1–3	3 days/week for 3 months	Not reported	1 set of 10 repetitions	Trunk rotation, hip abduction, stretches of hamstrings, quadriceps, calves, ankles	Resistance Endurance	↑ muscle strength
Frazzitta et al	2014	RCT	PD PD-CG	1–1.5	5 days/week for 4 weeks	Not reported	1-h session	Relaxation and stretching of scapular, hip flexor, hamstring, calf; ROM stretches	Endurance Balance-gait exercise Occupational therapy	↑ BDNF and motor performance
Ellis et al	2016	Guideline	PD	Not reported	3–4 repetitions for each stretch 2–3 times/week or daily	Do not bounce, do not stretch to the point of pain	30–60 s	Hip flexor, trunk twist, hamstring step stretch, calf stretch, yoga, passive stretch	Resistance Balance Endurance	↑ stiffness ↑ muscle spasms
Riebe et al	2018	Guideline	PD	1–3	≥2–3 days/week or daily	Full extension, rotation, flexion or stretch to the point of discomfort	Hold static stretch for 10–30 s; 2–4 repetitions of each exercise	Slow static stretches for major muscle groups	Aerobic Resistance	↑PD progression
Oliveira de Carvalho et al	2018	Review	PD	1–3	2–3 days/week	To the point of discomfort	10–30 s	Static stretches, dynamic, PNF, spine-trunk stretches	Aerobic, resistance, balance	↑ motor signs ↑ brain plasticity

PD Parkinson disease, *CG* control group, *L-DOPA* Levodopa, *RCT* randomized controlled trial, *PNF* proprioceptive neuromuscular facilitation, *ROM* range of motion, *BDNF* brain-derived neurotrophic factor

Table 12 Interaction between exercise and medication

Author	Year	Design	Subject	H&Y stage	Drug	Medication status	Exercise modality	Protocol	Result
Carter et al	1992	Research study	PD	Not reported	L-DOPA	On medication	Cycle ergometer	L-DOPA + Training L-DOPA at rest	no difference > absorption < absorption
Goetz et al	1993	RCT	PD-vigorous PD-no exercise	Not reported	L-DOPA	On medication	Modified Naughton protocol on treadmill	Vigorous exercise No exercise	Better UPDRS in both groups Absorption not influenced by exercise if drug taken 60 min before exercise
Reuter et al	2000	Clinical trail	PD	2–3	L-DOPA	On medication	Cycle ergometer	Baseline 2hours at 50Watts	Better absorption Deteriorated absorption
Muhlak et al	2007	Review	PD	1–2	L-DOPA	On medication	Cycle ergometer	Training Rest	No significant differences
DiFrancisco-Donoghue et al	2009	Clinical trial	PD CG	2	L-DOPA	On medication Off medication	Modified Bruce protocol on treadmill	Maximum of five 3 min intervals	< HR, NE, BP in PD
Lopane et al	2010	RCT	PD	2–3	L-DOPA	On medication	Cycle ergometer	L-DOPA + 15 min at moderate intensity L-DOPA at rest	No significative effects by exercise
Klemann et al	2018	Research study	PD Mice Control Mice	Not reported	None	None	Treadmill	30 min twice daily for 3 weeks	RICTOR, L-DOPA, CREB1 genes altered with exercise

PD Parkinson disease, *CG* control group, *L-DOPA* Levodopa, *RCT* randomized controlled trial, *UPDRS* Unified Parkinson Disease Rating Scale, *HR* heart rate, *NE* norepinephrine, *BP* blood pressure

Table 13 General Recommendations: clinical testing and training for Early PD diagnosis

	Clinical test	Frequency training	Intensity training	Time training	Type training
Endurance	TUG; Tinetti Balance and Gait Test; RPT; SLST; FRT; BESTest; Mini-BESTest; BBS	3 days/week	Vigorous: 60–89% of HRR, 14–17 on 6–20 RPE scale	45 min	Prolonged activities, running, cycling, swimming, walking over a variety of terrains and obstacles
Resistance	HST; Isokinetic Strength Test; MMT; ACT; CST; FTSTS; 1-RM	3 days/week	High: 60–80% 1-RM	2–4 sets, 8–12 repetitions	Major muscle groups exercise, weight machines, other resistance devices, free weights
Flexibility	Goniometer; Inclinometer; Leighton flexometer; SRT; BST	30 min/day	Not beyond the point of discomfort	60 s for each of the 3 repetitions	Major muscle group and calf stretches, prone lying, static stretches

HRR heart rate reserve, *RPE* rate of perceived exertion, *TUG* Timed Up and Go Test, *RPT* Retropulsion Test, *SLST* One-leg Stance Test, *FRT* Åstrand-Rhyming protocol during Graded Exercise Test, *BESTest* Balance Evaluation System Test, *Mini-BESTest* Mini Balance Evaluation Systems Test, *BBS* Berg Balance Scale, *HST* Handgrip Strength Test, *MMT* Manual Muscle Test, *ACT* Arm Curl Test; Chair Stand Test; Five Time Sit to Stand Test; *1-RM* one Repetition Maximum, *SRT* Sit and Reach Test, *BST* Back Scratch Test

Table 14 General Recommendations: clinical testing and training for Moderate PD diagnosis

	Clinical testing	Frequency training	Intensity training	Time training	Type training
Endurance	TUG; Tinetti Balance and Gait Test; RPT; SLST; FRT; BESTest; Mini-BESTest; BBS	Daily	Moderate: 40–59% HRR, 12–13 on 6–20 RPE scale	30–40 min in multiple sessions	Walking, cycling, swimming over a variety of terrains, obstacles under supervision and attentional cues
Flexibility	HST; Isokinetic Strength Test; MMT; ACT; CST; FTSTS; 1-RM	30 min/day	Not beyond the point of discomfort	30–60 s for each of the 3 repetitions	Calf stretches while standing, prone lying and positioning program
Resistance	Goniometer; Inclinometer; Leighton flexometer; SRT; BST	2–3 days/week	Very light: < 30 1-RM	≥ 1 sets, 10–15 repetitions	Avoid free weights, Supervised stair climbing, repetitive stepping, orthosis

HRR heart rate reserve, *RPE* rate of perceived exertion, *1-RM* one repetition maximum, *TUG* Timed Up and Go Test, *RPT* Retropulsion Test, *SLST* One-leg Stance Test, *FRT* Åstrand-Rhyming protocol during Graded Exercise Test, *BESTest* Balance Evaluation System Test, *Mini-BESTest* Mini Balance Evaluation Systems Test, *BBS* Berg Balance Scale, *HST* Handgrip Strength Test, *MMT* Manual Muscle Test, Arm Curl Test; Chair Stand Test; Five Time Sit to Stand Test, *1-RM* one Repetition Maximum, *SRT* Sit and Reach Test, *BST* Back Scratch Test

Table 15 General recommendations: clinical testing and training for Advanced PD diagnosis

	Clinical testing	Frequency training	Intensity training	Time training	Type training
Endurance	Tinetti Balance and Gait Test; RPT; SLST; FRT; BESTest; Mini-BESTest	Daily	Light: 30–59 of HRR, 9–11 on 6–20 RPE scale	20 min or multiple sessions of 10 min	Walking under supervision, with assistive devices and palliative approaches, stationary cycle, arm ergometer with safety harness
Resistance	MMT; FTSTS	2–3 days/week	Very light: < 30 1-RM	≥ 1 sets, 10–15 repetitions	Avoid free weights Supervised stair climbing, repetitive stepping, orthosis
Flexibility	Goniometer; Inclinometer; Leighton flexometer; SRT; BST	15 min twice a day	Not beyond the point of discomfort	10–30 s for each repetition	Assisted calf stretches while standing, hamstring stretches while sitting, lying supine or prone

PD Parkinson disease, *HRR* heart rate reserve, *RPE* rate of perceived exertion, *1-RM* one repetition maximum, *RPT* Retropulsion Test, *SLST* One-leg Stance Test, *FRT* Åstrand-Rhyming protocol during Graded Exercise Test, *BESTest* Balance Evaluation System Test, *Mini-BESTest* Mini Balance Evaluation Systems Test, *MMT* Manual Muscle Test; Five Time Sit to Stand Test, *1-RM* one repetition maximum, *SRT* Sit and Reach Test, *BST* Back Scratch Test

to confirm the results and to transform them into appropriate guidelines for patients with severe disease. Furthermore, future studies that clarify the sensitivity, and reliability of the assessments, as well as the compliance of patients with PD in joining different training programs are strongly needed, to improve the choice of appropriate clinical tests, protocols and the understanding of their outcomes.

Conclusions

For this review, we collected data from recently published studies that investigated physical training as a significant non-pharmacological treatment for neurodegeneration in PD. We aimed to find the most appropriate and suitable clinical tests for each disease stage and to identify the impairments to be treated with training according to each PD level. To date, there are no solutions to completely avoid drug prescription nor a standard exercise protocol to be broadly offered to patients. General modalities of exercise such as endurance training, resistance training, and flexibility training are increasingly recognized to alleviate symptoms in PD and thus improve quality of life; on the other hand, uncertainty and insufficient data remain about the interaction between exercise and drug delivery, especially for pharmacokinetics and pharmacodynamics.

A future area of focus is the correct FITT of exercise that can be personalized according to disease stage and

drug dose. For now, it seems that the most effective training protocol is the one that combines multiple exercise modalities to be performed routinely during the week and in the long term, to maintain benefits on endurance, resistance, and flexibility (Tables 13, 14, 15). Hence, patients can manage symptoms and improve their general health. However, because PD is an irreversible and progressive disease, patients will require regular monitoring with specific clinical and exercise-test evaluations and adjustments to their training protocols and therapeutic plans based on symptom-related changes over time.

Author contributions MC reviewed the literature, collected the data and drafted the manuscript; AP, MV, GG, FR and FGL revised and edited it critically; AP, MV, FS, MT, RBM and JJF supervised the manuscript. All authors approved the final version.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any experimental study with humans or animals performed by the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Dorsey ER, Elbaz A, Nichols E et al (2018) Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 17:939–953. https://doi.org/10.1016/s1474-4422(18)30295-3
2. Magrinelli F, Picelli A, Tocco P et al (2016) Pathophysiology of motor dysfunction in Parkinson's disease as the rationale for drug treatment and rehabilitation. Parkinsons Dis. https://doi.org/10.1155/2016/9832839
3. Abbas MM, Xu Z, Tan LCS (2018) Epidemiology of Parkinson's disease-east versus west. Mov Disord Clin Pract 5:14–28. https://doi.org/10.1002/mdc3.12568
4. Collamati A, Martone AM, Poscia A et al (2016) Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. Aging Clin Exp Res 28:25–35. https://doi.org/10.1007/s40520-015-0359-7
5. Hirsch MA, Farley BG (2009) Exercise and neuroplasticity in persons living with Parkinson's disease. Eur J Phys Rehabil Med 45:215–229
6. Kim JD, McCarter RJM, Yu BP (1996) Influence of age, exercise, and dietary restriction on oxidative stress in rats. Aging Clin Exp Res 8:123–129. https://doi.org/10.1007/BF03339566
7. Reuter I, Engelhardt M, Stecker K et al (1999) Therapeutic value of exercise training in Parkinson's disease. Med Sci Sports Exerc 31:1544–1549
8. Suchowersky O, Gronseth G, Perlmutter J et al (2006) Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 66:976–982. https://doi.org/10.1212/01.wnl.0000206363.57955.1b
9. Kwakkel G, De Goede C, Van Wegen E (2007) Impact of physical therapy for Parkinson's disease: a critical review of the literature. Parkinson Relat D 13:478–487. https://doi.org/10.1016/S1353-8020(08)70053-1
10. Schenkman M, Moore CG, Kohrt WM et al (2018) Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo parkinson disease: a phase 2 randomized clinical trial. JAMA Neurol 75:219–226. https://doi.org/10.1001/jamaneurol.2017.3517
11. Riebe D, Ehrman JK, Liguori JK et al (2018) ACSM's guidelines for exercise testing and prescription, 10th ed
12. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62:e1–34. https://doi.org/10.1016/j.jclinepi.2009.06.006
13. Redecker C, Bilsing A, Csoti I et al (2014) Physiotherapy in Parkinson's disease patients: recommendations for clinical practice. Basal Ganglia 4:35–38. https://doi.org/10.1016/j.baga.2014.03.001
14. Opara JO, Małecki A, Małecka E et al (2017) Motor assessment in Parkinson's Disease. Ann Agric Environ Med 24(3):441–451. https://doi.org/10.5604/12321966.1232774
15. Gallo PM, Ewing Garber C (2011) A comprehensive approach to exercise prescription for the health fitness professional. ACSMs Health Fit J 15:8–17. https://doi.org/10.1249/fit.0b013e31821eca84
16. Rebelo-Marques A, De Sousa Lages A, Andrade R (2018) Aging hallmarks: the benefits of physical exercise. Front Endocrinol 9:258. https://doi.org/10.3389/fendo.2018.00258
17. Ellis T, Rochester L (2018) Mobilizing Parkinson's disease: the future of exercise. J Parkinsons Dis 8:S95–S100. https://doi.org/10.3233/JPD-181489
18. Dos Santos Delabary M, Komeroski IG, Monteiro EP et al (2018) Effects of dance practice on functional mobility, motor symptoms and quality of life in people with Parkinson's disease: a systematic review with meta-analysis. Aging Clin Exp Res 30:727–735. https://doi.org/10.1007/s40520-017-0836-2
19. Bryant MS, Jackson GR, Hou JG et al (2016) Treadmill exercise tests in persons with Parkinson's disease: responses and disease severity. Aging Clin Exp Res 28:1009–1014. https://doi.org/10.1007/s40520-015-0498-x
20. Oliveira de Carvalho A, Filho ASS, Murillo-Rodriguez E et al (2018) Physical exercise for Parkinson's disease: clinical and experimental evidence. Clin Pract Epidemiol Ment Health 14:89–98. https://doi.org/10.2174/1745017901814010089
21. Noonan V, Dean E (2000) Submaximal exercise testing: clinical application and interpretation. Phys Ther 80:782–807
22. Mavrommati F, Collett J, Franssen M et al (2017) Exercise response in Parkinson's disease: insights from a cross-sectional comparison with sedentary controls and a per-protocol analysis of a randomised controlled trial. BMJ Open 7:e017194. https://doi.org/10.1136/bmjopen-2017-017194
23. Penko AL, Barkley JE, Miller Koop M et al (2017) Borg scale is valid for ratings of perceived exertion for individuals with Parkinson's disease. Int J Exerc Sci 10:76–86

24. Mancini M, Horak FB (2010) The relevance of clinical balance assessment tools to differentiate balance deficits. Eur J Phys Med 46:239–248
25. Chomiak T, Pereira FV, Hu B (2015) The single-leg-stance test in Parkinson's disease. J Clin Med Res 7:182–185. https://doi.org/10.14740/jocmr1878w
26. Jacobs JV, Horak FB, Tran VK et al (2006) Multiple balance tests improve the assessment of postural stability in subjects with Parkinson's disease. J Neurol Neurosurg Psychiatry 77:322–326. https://doi.org/10.1136/jnnp.2005.068742
27. Brusse KJ, Zimdars S, Zalewski KR et al (2005) Testing functional performance in people with Parkinson disease. Phys Ther 85:134–141
28. Bloem BR, Marinus J, Almeida Q et al (2016) Measurement instruments to assess posture, gait, and balance in Parkinson's disease: critique and recommendations. Mov Disord 31:1342–1355. https://doi.org/10.1002/mds.26572
29. Keus S, Munneke M, Graziano M et al (2014) European Physiotherapy Guideline for Parkinson's Disease Developed with twenty European professional associations Development and scientific justification, ParkinsonNet KNGF
30. White DK, Wagenaar RC, Ellis TD et al (2009) Changes in walking activity and endurance following rehabilitation for people with Parkinson disease. Arch Phys Med Rehabil 90:43–50. https://doi.org/10.1016/j.apmr.2008.06.034
31. Light KE, Behrman AL, Thigpen M et al (1997) The 2-minute walk test: a tool for evaluating walking endurance in clients with Parkinson's disease. Neurol Rep 20:136–139
32. Goodwin VA, Richards SH, Taylor RS et al (2008) The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Mov Disord 23:631–640. https://doi.org/10.1002/mds.21922
33. Durmus B, Baysal O, Altinayar S et al (2010) Lower extremity isokinetic muscle strength in patients with Parkinson's disease. J Clin Neurosci 17:893–896. https://doi.org/10.1016/j.jocn.2009.11.014
34. Clael S, Brandao E, Caland L et al (2018) Association of strength and physical functions in people with Parkinson's disease. Neurosci J 2018:8507018. https://doi.org/10.1155/2018/8507018
35. Frazzitta G, Ferrazzoli D, Maestri R et al (2015) Differences in muscle strength in parkinsonian patients affected on the right and left side. PLoS ONE 10:3. https://doi.org/10.1177/1545968313508474
36. Koller W, Kase S (1986) Muscle strength testing in Parkinson's disease. Eur Neurol 25:130–133. https://doi.org/10.1159/000115998
37. Lombara A (2017) Parkinson's disease: an overview. Phys Ther 20:20
38. Cancela JM, Ayán C, Gutiérrez-Santiago A et al (2012) The Senior fitness test as a functional measure in Parkinson's disease: a pilot study. Parkinson Relat Disord 18:170–173. https://doi.org/10.1016/j.parkreldis.2011.09.016
39. Buckley TA, Hass CJ (2012) Reliability in one-repetition maximum performance in people with Parkinson's disease. Parkinsons Dis. https://doi.org/10.1155/2012/928736
40. Zoladz JA, Majerczak J, Zeligowska E et al (2014) Moderate-Intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in Parkinson's disease patients. J Physiol Pharmacol 65:441–448
41. Harvey M, Weston KL, Gray KG et al (2019) High-intensity interval training in people with Parkinson's disease: a randomized, controlled feasibility trial. Clin Rehabil 33:428–438. https://doi.org/10.1177/0269215518815221
42. Shulman LM, Katzel LI, Ivey FM et al (2013) Randomized clinical trial of 3 types of physical exercise for patients with Parkinson disease. JAMA Neurol 70:183–190. https://doi.org/10.1001/jamaneurol.2013.646
43. Kim Y, Lai B, Mehta T et al (2019) Exercise training guidelines for multiple sclerosis, stroke, and Parkinson disease: rapid review and synthesis. Am J Phys Med Rehabil 98:613–621. https://doi.org/10.1097/PHM.0000000000001174
44. Nelson R, Petersen C (2017) The reliability and minimal detectable change of the cardiovascular response and self-selected exercise intensity during forward and backward treadmill exercise in individuals with Parkinson disease. SAGE Open Med. https://doi.org/10.1177/2050312117736229
45. Speelman AD, Groothuis JT, van Nimwegen M et al (2012) Cardiovascular responses during a submaximal exercise test in patients with Parkinson's disease. J Parkinsons Dis 2:241–247. https://doi.org/10.3233/JPD-2012-012111
46. H. Cianci (2012) A body guide to Parkinson's Disease, Fitness Count
47. McGraw SM, Hoover DL, Shirey MP (2013) Exercise guidelines for patients with Parkinson's disease. Home Health Care Manag Pract 26:167–174. https://doi.org/10.1177/1084822313514977
48. Nadeau A, Pourcher E, Corbeil P (2014) Effects of 24 wk of treadmill training on gait performance in Parkinson's disease. Med Sci Sports Exerc 46:645–655. https://doi.org/10.1249/MSS.0000000000000144
49. Salgado S, Williams N, Kotian R (2013) An evidence-based exercise regimen for patients with mild to moderate Parkinson's disease. Brain Sci 3:87–100. https://doi.org/10.3390/brainsci3010087
50. Miyai I, Fujimoto Y, Ueda Y (2000) Treadmill training with body weight support: its effect on Parkinson's disease. Arch Phys Med Rehabil 81:849–852. https://doi.org/10.1053/apmr.2000.4439
51. Hou L, Chen W, Liu X (2017) Exercise-induced neuroprotection of the nigrostriatal dopamine system in Parkinson's disease. Front Aging Neurosci 9:358. https://doi.org/10.3389/fnagi.2017.00358
52. Ahlskog JE (2018) Aerobic exercise: evidence for a direct brain effect to slow Parkinson Disease progression. Mayo Clin Proc 93:360–372. https://doi.org/10.1016/j.mayocp.2017.12.015
53. Frazzitta G, Maestri R, Ghilardi MF (2014) Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: a randomized study. Neurorehabil Neural Repair 28:163–168. https://doi.org/10.1177/1545968313508474
54. Fisher BE, Wu AD, Salem GJ et al (2008) The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. Arch Phys Med Rehabil 89:1221–1229. https://doi.org/10.1016/j.apmr.2008.01.013
55. Steiger L, Homann CN (2019) Exercise therapy in Parkinson's disease—an overview of current interventional studies. Physiother Res Rep 1:1–10. https://doi.org/10.15761/PRR.1000117
56. Uhrbrand A, Stenager E, Pedersen MS et al (2015) Parkinson's disease and intensive exercise therapy—a systematic review and meta-analysis of randomized controlled trials. J Neurol Sci 353:9–19. https://doi.org/10.1016/j.jns.2015.04.004
57. Hirsch MA, Toole T, Maitland CG et al (2003) The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease11No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors(s) or upon any organization with which the author(s) is/are associated. Arch Phys Med Rehab 84:1109–1117. https://doi.org/10.1016/s0003-9993(03)00046-7
58. EllisT, DeAngelis TR, Dalton D, Venne J (2016) Be active & beyond—a guide to exercise and wellness for people with Parkinson's Disease
59. Petersen CM, Nelson R, Steffen TM (2013) The effect of Parkinson drug timing on cardiovascular response during treadmill

exercise in a person with Parkinson Disease and freezing of gait. Physiother Can 65:217–222. https://doi.org/10.3138/ptc.2011-57
60. Marsden CD, Parkes JD (1977) Success and problems of long-term levodopa therapy in Parkinson's disease. Lancet 20:345–349
61. Lopane G, Contin M, Scaglione C et al (2010) The effect of a clinically practical exercise on levodopa bioavailability and motor response in patients with Parkinson disease. Clin Neuropharmacol 33:254–256. https://doi.org/10.1097/WNF.0b013e3181f5328c
62. Reuter I, Harder S, Engelhardt M et al (2000) The effect of exercise on pharmacokinetics and pharmacodynamics of levodopa. Mov Disord 15:862–868. https://doi.org/10.1002/1531-8257(200009)15:5<862:AID-MDS1015>3.0.CO;2-S
63. Carter JH, Nutt JG, Woodward WR (1992) The effect of exercise on levodopa absorption. Neurology 42:2042–2045. https://doi.org/10.1212/wnl.42.10.2042
64. Muhlack S, Welnic J, Woitalla D et al (2007) Exercise improves efficacy of levodopa in patients with Parkinson's disease. Mov Disord 22:427–430. https://doi.org/10.1002/mds.21346
65. DiFrancisco-Donoghue J, Elokda A, Lamberg E (2009) Norepinephrine and cardiovascular responses to maximal exercise in Parkinson's disease on and off medication. Mov Disord 24:1773–1778. https://doi.org/10.1002/mds.22612
66. Skidmore FM, Patterson SL, Shulman LM et al (2008) Pilot safety and feasibility study of treadmill aerobic exercise in Parkinson disease with gait impairment. J Rehabil Res Dev 45:117–124. https://doi.org/10.1682/JRRD.2006.10.0130
67. Cotman CW, Berchtold NC (2002) Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 25:295–301. https://doi.org/10.1016/S0166-2236(02)02143-4
68. Klemann CJHM, Xicoy H, Poelmans G et al (2018) Physical exercise modulates L-DOPA-regulated molecular pathways in the MPTP mouse model of Parkinson's disease. Mol Neurobiol 55:5639–5657. https://doi.org/10.1007/s12035-017-0775-0
69. Dibble LE, Lange M (2006) Predicting falls in individuals with Parkinson disease: a reconsideration of clinical balance measures. J Neurol Phys Ther 30:60–67. https://doi.org/10.1097/01.npt.0000282569.70920.dc
70. O'Callaghan A, Harvey M, Houghton D et al (2019) Comparing the influence of exercise intensity on brain-derived neurotrophic factor serum levels in people with Parkinson's disease: a pilot study. Aging Clin Exp Res. https://doi.org/10.1007/s40520-019-01353-w
71. Macleod AD, Counsell CE (2010) Timed tests of motor function in Parkinson's disease. Parkinson Relat Disord 16:442–446. https://doi.org/10.1016/j.parkreldis.2010.04.006
72. Dibble LE, Foreman KB, Addison O et al (2015) Exercise and medication effects on persons with Parkinson disease across the domains of disability: a randomized clinical trial. J Neurol Phys Ther 39:85–92. https://doi.org/10.1097/NPT.0000000000000086