Physiotherapy Research and Reports

Review Article

ISSN: 2516-7081

Exercise therapy in Parkinson's disease – An overview of current interventional studies

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Abstract

Background: Morbus Parkinson is a progressive neurodegenerative disorder and is considered to be one of the most common neurological diseases. The treatment of typical motor and non-motor symptoms with pharmacological and neurosurgical interventions is limited to some extent. Exercise therapy represents a supplementary treatment option. Although there are more and more studies investigating exercise therapy in Parkinson's disease, there is a lack of precise recommendations on exercise modality, duration and intensity.

Objective: The objective of this study is to provide an overview of current interventional studies on exercise therapy in Parkinson's disease, to present exercise programs of effective studies in detail for practice-oriented application and to develop precise exercise recommendations.

Methods: In February 2018 a systematic literature search of current interventional exercise studies in Parkinson's disease of the last ten years was performed using the database PubMed.

Results: Twenty-eight studies (with overall 1314 patients) with different types of exercise (endurance, strength, balance, tai chi etc.) were included in this study, whereby 22 studies used endurance or strength training. Twenty-five studies reported positive effects of the intervention. Except for four studies only participants with mild to moderate disease severity (Hoehn and Yahr stage 1-3) were investigated. Data about exercise intensity was reported heterogeneously. No study reported severe negative side effects.

Conclusion: Overall, exercise therapy seems to be a safe and effective additional treatment option in Parkinson's disease. The following exercise recommendations are based on the effective exercise intervention programs of the included studies and are aimed to improve motor and some non-motor symptoms of Parkinson's disease (in Hoehn and Yahr stage 1-3): Per week people with Parkinson's disease should perform 1) two sessions of endurance training of 30 to 60 minutes duration per session, 2) two sessions of strength training and 3) two sessions of either balance training or tai chi. Future studies should focus on different exercise intensities and modalities (e.g. strength training on unstable surfaces, high-speed strength training) and the underlying physiological responses in Parkinson`s disease.

Introduction

Parkinson's disease (PD) is amongst the most common neurological diseases worldwide, affecting around ten million people [1] and is showing a steady increase of prevalence with age [2]. Men seem to have a slightly higher risk for PD than women [3]. The disease is characterized by the motor-symptoms tremor, rigidity and bradykinesia [4] with a wide range of non-motor symptoms that can appear sooner or later in the course of the disease [5]. The underlying pathology of PD is found in the loss of neurons of substantia nigra with dopaminergic denervation of the striatum [6]. Etiology is not sufficiently clarified, so that for now reasons for development of PD are thought to be multifactorial [7]. Treatment options range from a broad spectrum of pharmacotherapies, with standard drug L-Dopa, to surgical interventions such as deep brain stimulation [8].

Exercise therapy as additional treatment option for PD has gained more and more interest in the past years, as measured by the steadily increasing number of interventional exercise training studies in PubMed. The potential of exercise training to improve symptoms of PD generally seems to be recognized [9]. The International Parkinson and Movement Disorder Society even emphasizes the importance and advantages of physical activity in PD [10]. However, questions about optimal exercise programs for improving symptoms of PD, or specific recommendations for prescription of optimal type of exercise, intensity or frequency are yet to be answered [9,11].

This literature review has three main purposes. First, to provide an overview of current interventional studies on PD. The second purpose is to present exercise programs of effective studies in detail for practice-oriented application for people who work with PD patients. The third goal was to develop precise exercise recommendations based on the overall findings. Particular emphasis was placed on simple feasibility of exercise recommendations, which means that training can be performed with basic equipment and devices used in conventional exercise therapy.

Methods

Search strategy

In order to identify relevant articles, literature research was performed on electronic database PubMed in February 2018. Five separate targeted search runs were undertaken using the two filters "clinical trial" and "10 years" and the following keywords: "Exercise

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Key words: *exercise therapy, exercise training, parkinson's disease, strength, endurance, balance, tai chi, exercise protocols, exercise recommendations*

Received: April 04, 2019; **Accepted:** April 16, 2018; **Published:** April 19, 2018

therapy"; "exercise training"; "endurance training"; "strength training" and "balance training" combined with "parkinson". This specific search period was selected because of a noticeable increase in scientific literature investigating the effects of physical activity on PD in the past decade. 637 potentially relevant articles were found. The flowchart of study selection is shown in Figure 1.

Inclusion and exclusion criteria

Studies that met the following criteria were classified as irrelevant: a) No exercise intervention; b) no purely movement-related activity (e.g. exercise combined with transcranial magnetic stimulation, dual-task training, visually/acoustically augmented training); c) technology-based intervention (e.g. exergaming, robot assisted training); d) intervention shorter than four weeks; e) no investigation of PD; f) study protocol. Subsequently, full text analysis of 73 articles was performed. To be included in this review, studies had to meet the following criteria: a) Exercise intervention study in patients with PD; b) the outcome measures reflected physiological responses due to exercise; c) measurements were conducted pre- and post-intervention; d) the exercise program was described in detail and comprehensible. Particular attention was paid to the availability of information on intensity, repetition number, training devices and other exercise specifications. Studies were excluded if: a) the intervention included a multimodal program (e.g. music therapy, behavioral therapy, breathing exercises, specific training of everyday activities or speech therapy); b) special equipment was necessary (e.g. antigravity treadmill, underwater exercise therapy, treadmill with body weight support system or virtual reality training); c) the intervention was a rather uncommon type of exercise (e.g. Irish set dancing) or hardly reproducible (e.g. dance class); d) passive exercises/therapies were part of the intervention. In the end, 28 interventional studies were included for the purpose of this review.

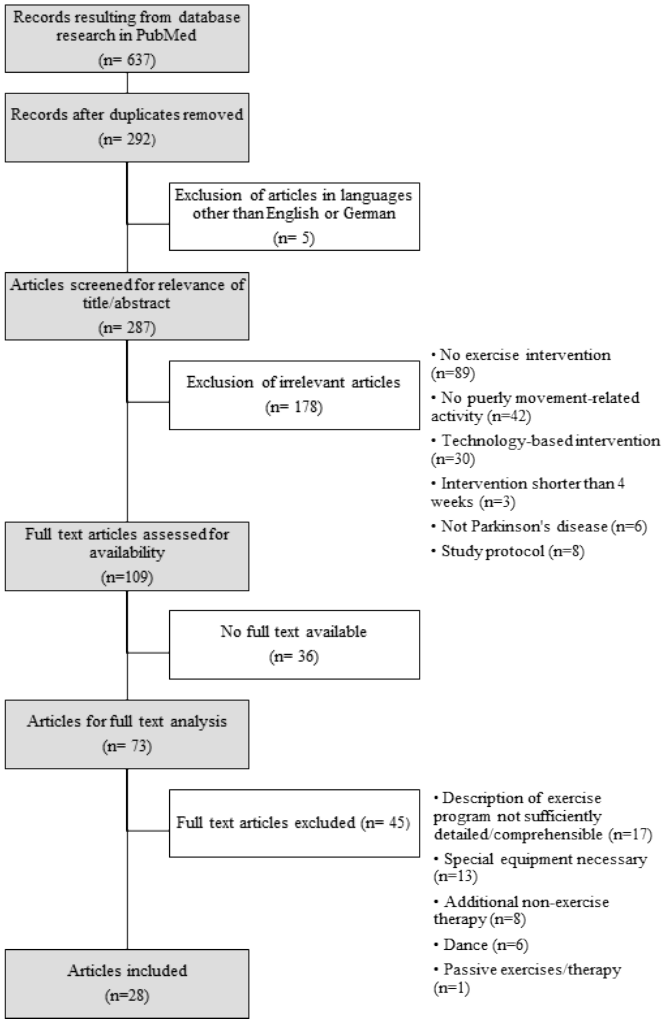

Figure 1. Flow chart of study selection

It should be noted that both studies with and without control group were included. It is the authors' view that relevant conclusions for an effective exercise program can also be drawn from studies without control group. This also applies to the comparison of different types of exercise (e.g. comparison of strength training with endurance training group). Furthermore, PD patients of any age and regardless of the duration or severity of the disease were included.

Data extraction

In order to provide an overview of the included studies, the following characteristics were extracted and summarized in table 1: Participant characteristics: Disease severity indicated in Hoehn and Yahr scale, total number, mean age, number of male and female participants; intervention characteristics: Duration of the intervention, number of exercise sessions per week and duration of each session, type of exercise of the intervention group, details of control group, overall outcome (effective/non-effective exercise program). In most studies, it was clear from the results whether the intervention led to overall positive effects on the disease. In unclear cases, such as presence of several outcome parameters with differing results, the overall outcome of the intervention was assessed based on a synopsis of the individual outcome results. This approach implies a certain degree of subjective assessment and therefore represents a limitation of this review.

One of the main purposes of this review was to provide detailed information on training contents of current, efficient exercise intervention programs in order to be able to develop own exercise programs for the work with PD patients. Therefore, the following data was extracted from the effective exercise intervention programs (depending on type of exercise): Exercise modality (e.g. interval training, continuous training), intensity, progression, warm-up and cool-down, repetition number, number of sets, names of exercises, training devices, breaks and any other exercise-relevant information.

Results

The descriptive data of the 28 included studies is shown in table 1. It has to be noted that four [25,31, 35,36] of the 28 studies were omitted for the description of study participants' characteristics, as these were subsequent studies.

Characteristics of study participants

Altogether, 1314 patients were included. The average age of the study participants was 65 years, ranging from 59 to 71 years. The smallest total number of participants in one study was 12 [39], while the largest study consisted of 231 participants [15] (Figure 2). The average sample size was 55. Of all participants 822 (63%) were male and 492 (37%) female. All studies included both men and women. PD severity was reported in all studies using the Hoehn and Yahr scale [40]. Mainly, PD patients with low to moderate disease severity (stage 1 to 3) took part in the intervention programs. Only four studies [15, 20, 24, 26] included more severely affected patients (stage 4).

Table 1. Descriptive data of the included studies

Study	HY	N	Age	Male/ female	Duration	Sessions per week	Intervention group	Control group	Result for intervention
Amano, 2013 [12]	2-3	45	66	28/17	16 we.	1) 2 SE à 60 min 2) 3 EH à 60 min	1) Tai chi 2) Tai chi	1) Qi gong meditation (2 SE à 60 min) 2) No intervention	No improvement
Atterbury, 2017 [13]	1-3	40	65	29/11	8 we.	3 SE à 40-60 min	1) Balance training with therapist 2) Balance training at home with DVD	None	Positive tendency (group with therapist better)
Bloomer, 2008 [14]	1-2	16	59	8/8	8 we.	2 SE	Strength training	No intervention	Positive tendency
Canning, 2015 [15]	2-4	231	71	135/96	6 mon.	3 SE à 40-60 min	Strength training for lower extremity and balance training	No intervention	No improvement
Carvalho, 2015 [16]	1-3	22	64	15/7	12 we.	1) 2 SE 2) 2 SE à 40 min 3) 2 SE à 40 min	1) Strength training 2) Endurance training 3) Physiotherapy	None	Positive tendency for strength and endurance training
Corcos, 2013 [17]	Ø 2,1	48	59	28/20	24 mon.	2 SE à 60-90 min	1) Progressive strength training 2) Non-progressive strength training, balance training and stretching	None	Group 1 significantly better than group 2
Cruise, 2011 [18]	1-3	28	60	18/10	12 we.	2 SE à 60 min	Combined strength and endurance training	No intervention	No improvement
Duchesne, 2015 [19]	1-2	39	66	21/18	12 we.	3 SE à 40 min	Endurance training	Healthy control with equal intervention	Significant improvements in both groups (INT similar improvements as CON)
Goodwin, 2011 [20]	1-4	130	65	74/56	10 we.	3 SE	Strength and balance training	No intervention	Positive tendency
Hackney, 2008 [21]	1,5-3	33	59	21/12	13 we.	2 SE à 60 min	Tai chi	No intervention	Positive tendency
Hass, 2012 [22]	1-3	18	71	14/4	10 we.	2 SE	Strength training	No intervention	Positive tendency
Kurtais, 2008 [23]	1-3	24	64	12/12	6 we.	3 SE à 40 min	Endurance training	No intervention	Positive tendency
Li, 2012 [24]	1-4	195	59	122/73	6 mon.	2 SE à 60 min	Tai chi	1) Strength training (2 SE à 60 min) 2) Stretching (2 SE à 60 min)	Significant improvement for tai chi vs. strength training and vs. stretching (Outcome: Postural instability)
Li, 2014 [25]	1-4	195	60	122/73	6 mon.	2 SE à 60 min	Tai chi	1) Strength training (2 SE à 60 min) 2) Stretching (2 SE à 60 min)	Positive tendency for tai chi and strength training (Outcome: Patient reported outcomes)
Monteiro, 2017 [26]	1-4	33	66	13/20	6 we.	2 SE à 35-50 min	1) Nordic walking 2) Walking (without poles)	None	Significant improvement for both groups (greater improvement in Nordic walking)
Nadeau, 2014 [27]	1,5-2	34	65	27/7	24 we.	3 SE à 60 min	1) Treadmill with increase of speed 2) Treadmill with increase of speed and incline	Low-intensity exercises (2 SE à 60 min and 1 SE at home)	Significant improvement in both groups
Ni, 2016 [28]	1-3	24	59	13/11	12 we.	2 SE	High-speed strength training	No intervention	Significant improvement
Picelli, 2016 [29]	1-3	17	71	12/5	4 we.	3 SE à 45 min	Endurance training	No intervention	Significant improvement
Prodoehl, 2015 [30]	Ø 2,1	48	64	28/20	24 mon.	2 SE à 60-90 min	1) Progressive strength training 2) Non-progressive strength training, balance training and stretching	None	Significant improvement in both groups (no difference between groups)
Rafferty, 2017 [31]	Ø 2,1	48	59	28/20	24 mon.	2 SE à 60-90 min	1) Progressive strength training 2) Non-progressive strength training, balance training and stretching	Healthy control (cross-sectional)	Positive tendency in both groups (group 2 better than group 1 compared to healthy control)
Schlenstedt, 2015 [32]	2,5-3	32	60	21/11	7 we.	2 SE à 60 min	1) Strength training 2) Balance training	None	Significant improvement only in strength training (no difference between groups)
Shulman, 2013 [33]	2-3	67	66	50/17	3 mon.	3 SE	1) High-intensity treadmill training 2) Low-intensity treadmill training 3) Stretching and strength training	None	Significant improvement in group 1 and 2 in cardiovascular fitness, significant improvement in group 3 in strength

Silva-Batista, 2016 [34]	2-3	39	65	29/10	12 we.	2 SE	1) Strength training with instability 2) Strength training (without instability)	No intervention	Significant improvement only in group 1 (no significant difference between groups) (Outcome: Timed Up and Go)
Silva-Batista, 2017 [35]	2-3	39	64	29/10	12 we.	2 SE	1) Strength training with instability 2) Strength training (without instability)	No intervention	Significant improvement in both groups (group 1 better than group 2) (Outcome: Neuromuscular measures)
Silva-Batista, 2017 [36]	2-3	37	64	29/8	12 we.	2 SE	1) Strength training with instability 2) Strength training (without instability)	1) No intervention 2) Healthy control (cross-sectional)	Significant improvement in both groups (group 1 better than group 2) (Outcome: Neuronal measures)
Uc, 2014 [37]	1-3	43	67	30/13	6 mon.	3 SE à 45 min	1) Continuous endurance training 2) Interval endurance training	None	Positive tendency in both groups
Xiao, 2016 [38]	1-3	96	68	67/29	6 mon.	4 SE à 45 min	Qi gong and walking (walking 30 min per day)	Walking (30 min per day)	Significant improvement
Zoladz, 2014 [39]	1-3	12	70	7/5	8 we.	3 SE à 60 min	Interval endurance training	None	Significant improvement
HY: Hoehn and Yahr stage, **N**: total number of participants, **SE**: session, **INT**: intervention group, **CON**: control group									

Intervention characteristics

Regarding the type of exercise, most commonly, pure endurance training (36% of all included interventions) and pure strength training (25%) were investigated. Traditional far eastern forms of exercise (tai chi and qi gong, 14%) existed in four studies [12,21,24,38] and only two studies [13,32] conducted pure balance training (8%). Some studies used mixed exercise programs (17%), such as a combination of endurance and strength training. Overall, study designs were very heterogenous. Nine studies [13,16,17,26,30,32,33,37,39] had no control group. The other studies used either a control group without intervention (in the sense of usual care) [12,14,15,18,20-23,28,29,34-36], or another type of exercise intervention [12,24,25,27,38] for comparison. Some studies comprised different intervention groups [12,13,16,17,26,27,30-37] and a small number also included a healthy control group [19, 31,36].

Training programs ranged from four weeks to 24 months, whereby seven studies [15,17,24,27,30,37,38] lasted six months or longer. In most studies exercise frequency was either two or three days per week (Figure 3). In one intervention, patients trained four times per week [38] whereas there was no study with only one session per week. Except for some strength training programs, exercise session duration was reported in the studies. Sessions usually took between 40 and 60 minutes. In two studies [17,30] a session duration of up to 90 minutes was described.

Details of the effective exercise programs

Of the 28 included studies, 25 reported positive effects of the intervention or, in case of more than one intervention group, for at least one of the groups. Details of the effective exercise programs are shown in tables 2-6. Generally, the most frequently investigated outcome measures included gait, functional mobility and UPDRS III [41].

Details of the effective endurance training programs

Nine studies [16,19,23,26,27,29,33,37,39] with eleven exercise programs investigated the effects of endurance training on PD, with all of them leading to positive results. Training protocols of the eleven programs can be seen in table 2. Only in two programs [16,26] participants trained only two times per week, in all other programs three sessions per week were completed. Exercise session duration varied between 30 [16,33] and 50 minutes [26,33]. Usually, at the beginning, interventions started with a shorter exercise duration, with 15 minutes being the shortest starting time [33]. In most studies

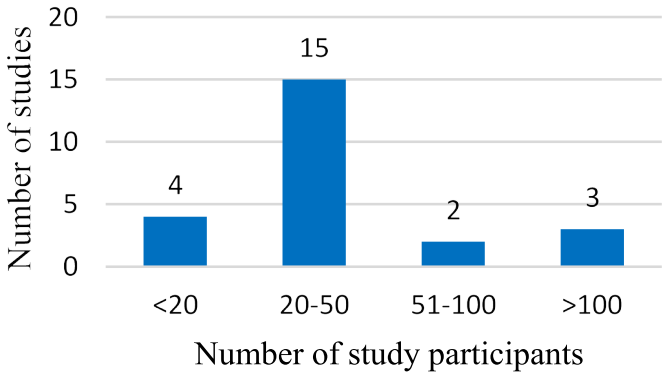

Figure 2. Number of study participants of the included studies

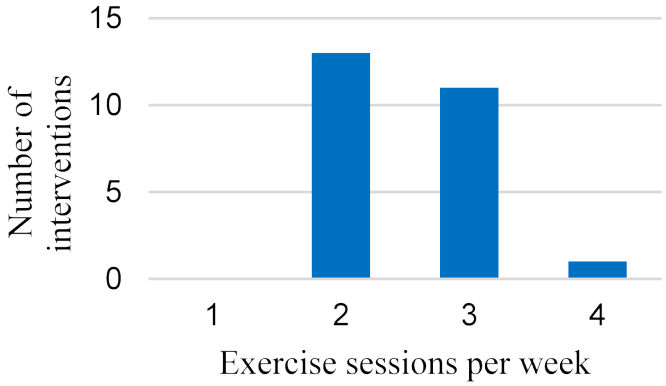

Figure 3. Number of exercise sessions per week. (In one study there were two intervention groups with different numbers of exercise sessions per week: Two and three, respectively. Therefore, regarding the number of exercise sessions per week, 25 instead of 24 interventions were considered).

training was performed on a treadmill ergometer, but also cycle [39] and recumbent [19] ergometers were used, or participants simply performed walking [26,37] or Nordic walking [26]. Regarding training method, in all but two programs, which used interval training [37,39], continuous training was applied. Only two studies [26, 39] provided detailed information on warm-up and cool-down.

Exercise intensity was reported heterogeneously. In some studies intensity was described in percentage of maximum heart rate (%

Table 2. Details of endurance training programs with positive effects

Study	SE/ we.	Character	Warm-up	Training details	Cool-down
Carvalho, 2015 [16]	2	Continuous endurance training on treadmill	5 min	●Duration: 30 min ●Walking on treadmill ●Intensity: 70 %HR max ●Progression: Increase of speed and/or treadmill incline to keep intensity constant	5 min
Duchesne, 2015 [19]	3	Continuous endurance training on recumbent bike	N/A	●Initial: 20 min with 60 %VO2max ●Intensity prescription based on VO2max test ●Progression: +5 min and +5 %VO2max per week ●Target intensity: 40 min with 80 %VO2max	N/A
Kurtais, 2008 [23]	3	Continuous endurance training on treadmill	Yes (not closer specified)	●Duration: 40 min ●Intensity: 70-80 %HR max ●Intensity prescription based on HR max test ●Progression: Increase of speed and/or treadmill incline to keep intensity constant	Yes (not closer specified)
Monteiro, 2017 [26]	2	Nordic Walking or walking (without poles)	3 min walking with self-selected speed	●Initial: 35 min with 60 %HRR or Borg RPE 13 ●Target: 50 min with 80 %HRR or Borg RPE 17 ●Progression: +5 %HRR and 5 min ca. every 3 sessions ●Intermittent recovery session after 4 weeks	5 min stretching
Nadeau, 2014 [27]	3	Continuous endurance training on treadmill with increase of speed or increase of speed plus incline	5 min (not closer specified)	●Duration: 45 min ●Walking on treadmill ●Intensity not more than 75 %HR max ●Initial: 80 % of self-selected speed, then increase up to 100 % ●Progression when Borg RPE 4 or less ●Progression: +0,2 km/h or + 1 % increase of treadmill incline and +0,2 km/h alternating	5 min (not closer specified)
Picelli, 2016 [29]	3	Continuous endurance training on treadmill	N/A	●Duration: 45 min ●Protocol: 10 min with 1 km/h – 5 min rest – 10 min with 1,5 km/h – 5 min rest – 10 min with 2 km/h	N/A
Shulman, 2013 [33]	3	Continuous endurance training on treadmill (high-intensity)	N/A	●Initial: 15 min with 40-50 %HRR ●Target: 30 min with 70-80 %HRR ●Progression: Every 2 weeks + 5min and + 0,2 km/h and/or +1 % increase of treadmill incline	N/A
Shulman, 2013 [33]	3	Continuous endurance training on treadmill (low-intensity)	N/A	●Initial: 15 min with self-selected speed ●Treadmill incline 0 % ●Progression: Every 2 weeks +5 min ●Target: 50 min with 40-50 %HRR	N/A
Uc, 2014 [37]	3	Continuous endurance training - walking	N/A	●Walking ●Duration: 45 min ●Progression from 15 to 45 min within 6 weeks ●Intensity: 70-80 %HR max (when taking beta-blockers HR max 20 % reduced)	N/A
Uc, 2014 [37]	3	Interval endurance training -walking	N/A	●Walking ●Duration: 45 min ●Progression from 15 to 45 min within 6 weeks ●Intervals: Alternating 3 min with 60-70 %HR max and 3 min with 80-90 %HR max	N/A
Zoladz, 2014 [39]	3	Interval endurance training on cycle ergometer	10 min cycling with self-selected speed	●Duration: 40 min ●Intervals: 8x3 min moderate intensity (80-90 rpm) and 2 min low intensity (under 60 rpm) ●Target for moderate intensity: 75 %HR max ●Initial: 60 %HR max ●Progression: 5 % every 2 weeks	10 min cycling with self-selected speed

SE: sessions, **%HRmax**: percent of maximum heart rate, **%HRR**: percent of heart rate reserve, **%VO2max**: percent of maximum oxygen uptake, **Borg RPE**: Received Perception of Exertion scale of Borg, **rpm**: rounds per minute

HR max) [16,23,27,37,39], whereas other studies used percentage of heart rate reserve (%HRR) for intensity description [26,33]. One study even reported intensity in percentage of maximum oxygen uptake (%VO2max) [19]. Target intensity of continuous endurance protocols ranged between 70 and 80 %HR max and 70 and 80 %HRR, respectively. Interval intensities were prescribed with even up to 90 %HR max [37]. In most studies, exercise intensity was kept constant throughout the intervention by increasing velocity or treadmill incline. Some studies, though, also progressed intensity. Uc et al. (2014) noted in their study that target intensity was reduced by 20 percent when taking beta-blockers [37].

Details of the effective strength training programs

In 13 studies [14,16,17,22,24,25,28,30-32,34-36] the effects of strength training on PD were investigated. Only one study [24] did not report on any improvements due to the strength training program. The effective strength training protocols are shown in table 3. In all studies participants trained two times per week, with a session duration, which was described in four studies [17,24,32,34], ranging from 40 [34] to 60 [17,24] minutes. All studies used progressive forms of strength training with adapting either weights, resistance and/or repetition number. Overall, regarding set number, repetition number, types of exercises or other details, exercise protocols were, due to the numerous variation possibilities in strength training, very heterogenous. Generally, all major muscle groups of the body [16,17,28,34] or only lower extremity muscle groups [14,22,25,32] were trained. Three studies [16,17,34] provided detailed information on warm-up and cool-down. Some studies conducted very complex and innovative exercise programs such as performing high-speed strength training [17], implementation of balance devices [34] or introducing agility-drills [28].

Details of the effective balance training programs

Only two studies conducted pure balance training [13,32] and just one of them proved to be effective [13] (table 4). In this program, progressive balance training was performed with increasing difficulty by introducing more and more unstable balance devices.

Details of the effective mixed training programs

Several studies combined different types of exercise in their intervention [15,17,18,20,30,31,33]. Due to the various possibilities of training compilation, generalization of common protocol details is not applied for this subcategory. Positive effects of the intervention were reported in four studies [20,30,31,33] (Table 5).

Details of the effective tai chi and qi gong training programs

Five studies investigated the effects of tai chi [12,21,24,25] or qi gong [38] on PD and four of them [21,24,25,38] showed positive results. Tai Chi programs were performed two times per week for 60 minutes per session [21,24] and qi gong was practiced even four times per week [38]. Details of the effective interventions are presented in table 6.

Adverse events and comorbidities of study participants

The majority of studies documented exercise-induced adverse events. However, degree of detail of the provided information varied from study to study. Overall, many studies stated that no exercise-

Table 3. Details of strength training programs with positive effects

Study	SE/ we.	Character	Warm-up	Training details	Cool-down
Bloomer, 2008 [14]	2	Progressive strength training with machines	N/A	●3 exercises: Leg press, seated leg curl, calf press ●3 sets of 5-8 rep ●Intensity: Every set to point where no more rep possible ●Progression: When 3 sets of 8 rep possible, increase of weight of 5-10 %	N/A
Carvalho, 2015 [16]	2	Progressive strength training with machines	1 set with low weight at beginning of every exercise	●5 exercises: Leg extensions, leg curls, leg presses, chest presses, low row ●2 sets of 8-12 rep ●Intensity: Every set to point where no more rep possible ●Progression: Initial 70-80 %1RM, then increase of weight to keep intensity constant	Stretching
Corcos, 2013 [17] Prodoehl, 2015 [30] Rafferty, 2017[31]	2	Progressive strength training and high-speed strength training	10 min: 3 min walking, then 5 stretching exercises: Neck circles, trunk rotation, arm circles, hamstring stretches, ankle stretches	●Duration: Ca. 60 min ●2 sets of 12 rep ●Intensity ca. 70-80 %1RM ●11 exercises: Chest press, latissimus pull downs, reverse flys, double leg press, hip extension, shoulder press, biceps curl, rotary calf (ankle plantar flexion), triceps extension, seated quadriceps extension, back extension ●Intensity initial: Ca. 30-40 %1RM for upper extremity exercises, 50-60 %1RM for lower extremity exercises ●3 sets of 8 rep (initial only 1 set) ●Progression: At least +5 % resistance when exercise „too easy" ●Every 8 weeks alternating to high-speed strength training ●Focus on fast movement speed	Same as warm-up
Hass, 2012 [22]	2	Progressive strength training with machines and resistance band	5 min (not closer specified)	●6 exercises with machines: Seated leg press, knee extension, knee flexion, abdominal curl, back extension, seated calf raises ●4 exercises for ankle joint (seated) with resistance band: Dorsiflexion, plantarflexion, inversion, eversion ●2 sets of 12-20 rep to point where almost no more rep possible ●After set 1 (every 10 exercises) 5 min rest ●Progression: Increase of weight/resistance to keep intensity constant	N/A
Li, 2014 [25]	2	Progressive strength training with free weights	N/A	●Duration: 60 min ●Exercises: Forward/side stepping, squats, forward/side lunges, heel/ toe raises ●1-3 sets of 10-15 rep ●Progression: Weighted vest, additional weights for ankle. Weighted vest initial 1 % of body weight, target: 5 %. Ankle weights initial 0,5 kg, target: 1,4 kg	N/A
Ni, 2016 [28]	2	Progressive high-speed strength training with machines	N/A	●11 exercises with pneumatically-controlled machines: Biceps curl, triceps pushdown, chest press, seated row, latissimus pull-down, shoulder press, leg press, leg curl, hip abduction, hip adduction, seated calf ●3 sets of 10-12 rep ●Alternating exercises for upper and lower extremity ●Progression: +5 % resistance when power-plateau unchanged in two consecutive sessions ●Concentric movements as fast as possible, eccentric movements slowly ●After 4 weeks change to 2 weeks translational training: Implementation of high-speed strength in balance exercises and agility-drills (with lines, cones, balls, agility ladder etc.)	N/A
Schlenstedt, 2015 [32]	2	Progressive strength training with free weights and own body weight	10 min (not closer specified)	●Duration: 50 min ●Exercises: Squats, knee extensions, toe/calf raises, hip abductions etc. ●Exercises for hip flexors/extensors/abductors, knee flexors/extensors, dorsi/ plantarflexion ●3 sets of 15-20 rep to point where almost no more rep possible ●2 min rest between sets ●Progression: Weighted vest, resistance band when 20 rep possible without problems	N/A
Silva-Batista, 2016 [34] Silva-Batista, 2017 [35, 36]	2	Progressive strength training with unstable surfaces	10 min cycle ergometer (20-40 rpm)	●Duration: 40 min ●Target: 4 sets of 6-8 rep ●First weeks: 2-3 sets of 10-12 rep ●Consecutive weeks: 3-4 sets of 8-10 rep ●2 min break between sets/exercises ●5 exercises: Leg press, latissimus dorsi pulldown, ankle plantarflexion, chest press, half squat ●Progression from stable to unstable surfaces: Balance pad, dyna discs, balance discs, BOSU® and Swiss ball (e.g. leg press: Balance pad (feet) → dyna discs (feet) and dyna disc (seat) → balance disc (feet) and balance disc (seat) → BOSU® (feet) and balance disc (seat) ●focus on correct movements, then increase of weight	N/A
SE: Sessions, **rep**: repetitions, **%1RM**: percent of One-Repetition-Maximum, **rpm**: rounds per minutes					

Table 4. Details of balance training programs with positive effects

Study	SE/ we.	Character	Warm-up	Training details	Cool-down
Atterbury, 2017 [13]	3	Progressive balance training	10 min	●Duration: 15-40 min ●Initial: Static postural control on unstable surfaces (with eyes closed, single leg stance, tandem stance, turning head, weight shift etc.) ●Progression: Dynamic postural control on unstable surfaces (movements with upper and lower extremity etc.) ●Progression: Functional balance (controlled steps, movements of daily life) ●Note: Verbal and tactile hints („pull shoulder blades together ", touching between shoulder blades etc.)	10 min relaxation techniques
SE: sessions					

induced adverse events occurred [20,24,27-29,33,34,37]. An interesting aspect was shown in the study of Canning et al. (2015) [15], in which PD patients in Hoehn and Yahr stages 2-4 performed combined strength and balance training three times per week. Subgroup analysis revealed that patients with lower disease severity had fewer falls due to the intervention, whereas patients with higher disease severity showed a tendency towards more falls.

Many studies excluded patients with certain diseases or chronic conditions other than PD. Very often, patients with a Mini Mental State Examination score lower than 23 [15,17,18,24,28,29,33,34,37,38] were excluded. Usually, also presence of preexisting cardiovascular diseases and certain orthopedic conditions was part of the exclusion criteria [13-17,20,23,28,32,34,37-39], though keeping those formulations very general.

Table 5. Details of mixed training programs with positive effects

Study	SE/ we.	Character	Warm-up	Training details	Cool-down
Goodwin, 2011 [20]	3 (1 SE under supervision, 2 SE at home)	Progressive strength and balance training	10 min: Marching, joint mobilization (arm swinging, rotating upper body, shoulder circles etc.)	●Duration: 40 min ●Balance: Side steps, side taps, side sway, lunges, toe walk, heel walk, tandem walk etc. ●Progression: Increase of step length, increase of range of motion, increase of repetitions, make stance more difficult etc. ●Strength: Heel raise, toe raise, sit to stand, seated leg press (with band), seated upper back strengthener (with band) etc. ●Progression: increase of repetitions, increase of resistance (band), make stance more difficult etc. ●Individual exercise program for home training	10 min stretching (calves, hamstrings etc.)
Prodoehl, 2015 [30] Rafferty, 2017 [31]	2	Strength training, balance training and stretching	10 min: 3 min walking, then 5 stretching exercises: Neck circles, trunk rotation, arm circles, hamstring stretches, ankle stretches	●Duration: Approx. 60 min ●12 stretching exercises: Standing chest stretch, seated neck and chest stretch, seated rotation stretch, overhead stretch, standing back stretch, hamstring stretch, lying shoulder stretch, seated side stretch, standing shoulder stretch, rotation stretch, calf stretch, ankle circles ●Stretching exercises each 3 times for 3-5 breaths ●6 strength exercises: Wall slides, bridging, shoulder blade squeeze, quadriceps strengthening (long arc quad), quadruped trunk strengthening (opposite arm/leg lifts), prone on elbows ●3 sets of 10 repetitions ●2 balance exercises: Body weight shift forwards/backwards (10-20 times), single leg stance (5-10 sec)	Same as warm-up
Shulman, 2013 [33]	3	Strength training and stretching	N/A	●First strength training then stretching ●3 strength exercises (with machines): Leg press, leg extension, leg curl ●2 sets of 10 repetitions per leg ●Increase of resistance to keep intensity constant ●Stretching exercises: Trunk rotation, hip abduction, stretches of hamstrings, quadriceps, calves, ankles	N/A
SE: sessions					

Table 6. Details of tai chi and qi gong training programs with positive effects

Study	SE/ we.	Character	Warm-up	Training details	Cool-down
Hackney, 2008 [21]	2	Tai chi	N/A	●Duration: 60 min ●Practicing of part 1 and 2 of Yang-style short form after Cheng Man Ching	N/A
Li, 2012 [24] 2014 [25]	2	Tai chi	N/A	●Duration: 60 min ●6 tai chi movements ●Specially targeted on balance, shifting of body weight, gait (side steps, forward/ backward steps, broad/narrow stance, upper body rotation etc.)	N/A
Xiao, 2016 [38]	4	Baduanjin qi gong and walking	N/A	●Duration: 45 min ●8 exercises of Baduanjin qi gong ●6 repetitions per exercise ●Duration of whole sequence approx. 15 min ●30 min walking per day	N/A
SE: sessions					

Discussion

The purpose of this review was to provide an overview of current interventional exercise studies on PD, to present exercise programs of effective studies in detail for practice-oriented application and to develop precise exercise recommendations for PD based on the overall findings. From the 28 included studies, almost all were effective in improving symptoms of PD. The finding that exercise training presents an effective additional therapy option in PD are consistent with other studies [42,43]. Moreover, the majority of studies documented adverse events with none of them reporting severe side effects. However, degree of detail of information on adverse events varied from study to study, which seems to be a common problem in evaluating safety aspects of exercise training in PD [44,45]. It should be noted that training was performed under supervision in nearly all interventions. Training at home without guidance might be associated with a higher risk of adverse events and should be evaluated in future studies.

The sample cohort included in this review almost exclusively comprises PD patients with mild to moderate disease severity. The main reason is that very often PD patients with a higher degree of disease severity (Hoehn and Yahr stages 4 and 5) are excluded from study participation a priori. Clearly, severe physical impairment complicates participation in exercise training programs. However, four of the included studies showed that PD patients in Hoehn and Yahr stage 4 can be integrated in exercise interventions [15,20,24,26]. One study provided indication that more severely affected PD patients might be more susceptive to exercise-related side effects [15]. To date, no study seems to have examined the effects of exercise training especially on more severely affected PD patients. Another noteworthy aspect of the results in this review concerns the presence of comorbidities. As preexisting cardiovascular diseases and orthopedic conditions or a MMSE score lower than 23 are amongst the exclusion criteria in many studies, the remaining sample cohort represents a physically fitter collective than it would be the case in the general population of PD. Therefore, exercise recommendations in this review might be too demanding especially for those presenting with comorbidities. In home exercise intervention studies it was shown that presence of comorbidities was associated with lower improvements [46] and performance of fewer exercise repetitions [47]. Exercise recommendations might also be too challenging for women, as only 37 percent of the sample cohort were female and therefore underrepresented. Percentage of gender distribution and age span of the included studies are similar to those of other reviews [45,48].

Interestingly, in the majority of endurance training interventions three sessions per week were clearly more often performed than two. Indeed, it was shown that three endurance training sessions per week with a duration of 60 minutes each are associated with even greater improvements in cognitive function than compared to two sessions [49]. It is supposed that endurance training can induce an increase of brain-derived neurotrophic factor and therefore positively influences cognitive function [50]. Furthermore, endurance training might contribute to reduction of depressive symptoms in PD [51]. Based on the details of the effective studies, two sessions per week for 30-60 minutes per session seem to be an appropriate dose as part of a full exercise program. Comparatively, other recommendations suggest performing endurance training every other day for up to 30 minutes per session [52]. However, target duration in all the here included studies is at least 30 minutes and therefore it cannot be evaluated whether positive effects also result from shorter session durations.

Due to the numerous design options in strength training, exercise protocols varied widely from study to study and therefore it was difficult to draw generally applicable conclusions. In other work it is recommended to perform strength training two to three times per week [52], or at least two times per week on non-consecutive days [44]. Overall, it seems that a session number of two times per week has proven to be most appropriate for strength training in PD. Strength training generally proved to be effective in improving strength [44,45,53], mobility and UPDRS III [44]. Similar results were found in the included studies of this review.

The reason why only one pure balance training study was included in this review, is primarily that nowadays balance training very often is conducted in form of exergaming, or with aid of technology-based systems. Those studies were excluded a priori because of the specially required devices, however, in future these exercise forms might play far more important roles in rehabilitation of PD than conventional training. For now, exergaming seems feasible in PD, but future studies are needed to confirm effectiveness and safety aspects [54]. Furthermore, balance training often is combined with other exercise forms. It is assumed that strength training in combination with balance training might be more effective than pure strength training [45]. Regarding tai chi training, it was shown that tai chi might particularly be suited to improve functional mobility and balance [55]. Generally, it is recommended to perform tai chi training two times per week for 60 minutes per session [43, 52].

Exercise recommendations

The following exercise recommendations are based on the results of the effective studies. It must be noted that these conclusions need to be interpreted carefully, as the underlying studies and this review itself have limitations. The recommendations aim at improving motoric and non-motoric symptoms of PD and only apply to patients in Hoehn and Yahr stages 1-3. It is recommended to perform training under qualified supervision. Exercise recommendations should always be adapted to the individual needs of patients.

Endurance training: ●) Two times per week; three times per week for greater effects especially on cognitive function, ●) session duration 30-60 minutes, ●) treadmill training is primarily recommended; alternatively walking or cycle ergometer (less data), ●) intensity 70-80 % HR max (ideally based on HRmax test); not applicable when taking heart rate affecting medication, ●) stepwise progression of intensity and duration is recommended, ●) progression via increase of speed or treadmill incline after ca. 3-6 sessions, ●) interval training seems feasible and effective in walking and on cycle ergometer (few data)

Strength training: ●) Two times per week; at least one day rest between sessions, ●) two to three sets per exercise, ●) 10-15 repetitions per set (as orientation, not always applicable), ●) approx. five to seven exercises per session; all major muscle groups of the body should be trained, ●) for selection of exercises see table 3, ●) intensity subjectively to the point where hardly any more repetitions can be performed ●) progression when more repetitions can easily be performed or when exercise feels too easy, ●) progression via increase of resistance, weight etc., ●) high-speed strength training seems feasible and effective (few data), ●) strength training on unstable surfaces seems feasible and more effective than equal training without unstable surfaces (few data), ●) stretching for cool-down is recommended, ●) for warm-up balance-exercises or few minutes on cycle ergometer or starting the first set with low intensity is recommended

Balance training and tai chi: ●) Balance training or tai chi two times per week, ●) e.g. 15 minutes balance exercises before strength training; otherwise two sessions of approx. 15 minutes duration per week, ●) for selection of exercises see tables 4 and 5, ●) alternatively two tai chi sessions per week can be recommended

Limitations

Generalizability of the results presented here is limited due to several reasons. The main problems were variability of outcome measures and heterogeneity of study designs. Some studies used one single measure as main outcome (e.g. 6 Minute Walking Test), while other studies combined several single measures in one main category (e.g. functional mobility), leaving sometimes room for interpretation concerning the effectiveness of interventions. This problem is also addressed in other work [52,56]. The problem of variable description of exercise details especially concerned intensity specifications in endurance training studies. It was not always clear if maximum heart rate was determined just mathematically or if a maximum heart rate test was performed. Inconsistency in reporting of intensity prescriptions also appeared in strength training studies, taking into account that strength training generally offers more design options. Overall, a more standardized reporting of training details would be necessary in order to facilitate comparability between studies.

Another weakness of this review presents the omission of potentially relevant studies due to the lack of free access. However, on the basis of similar interventions, study populations and outcomes indicated in the abstracts of those studies, it can be assumed that no substantial information was lost, or no differing exercise recommendations would have been derived.

Conclusion

Exercise training presents an effective additional therapy option for motor and non-motor symptoms in PD, however with uncertainties regarding optimal training design. Based on the effective training programs of current interventional studies on exercise therapy in PD, the following exercise recommendations were derived: Per week 1) two endurance training sessions of 30 to 60 minutes per session, 2) two strength training sessions and 3) two balance training sessions or two tai chi sessions should be performed. It must be noted that these recommendations are based on the results of a limited and selected number of studies. Future research is needed to firmly establish and develop optimal exercise prescriptions for PD. Particularly, certain exercise forms such as high-speed strength training or strength training on unstable surfaces might have a higher potential for improving PD-

specific symptoms like bradykinesia and postural instability than conventional training methods and therefore should be especially investigated. Furthermore, there is a lack of randomized controlled trials examining the effects of long-term training on the natural course of PD.

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