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Vastly Different Exercise Programs Similarly Improve Parkinsonian Symptoms: A Randomized Clinical Trial

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Keywords
Exercise specificity · Balance training · Posture · Quality of life

Abstract
Objectives: To directly compare the effects of agility exergaming (EXE) and stationary cycling (CYC) exercise training on Parkinson's disease (PD) patients' mobility and clinical symptoms. ***Design:*** Randomized clinical trial. ***Setting:*** Outpatient physiotherapy clinic in a hospital. ***Participants:*** Seventy-four stage 2–3, nondemented PD patients were included in this study. ***Intervention:*** The groups were as follows: EXE (n = 25), CYC (n = 25), and a wait-listed control group (CON; n = 24). The EXE and CYC groups exercised 5×/week for 5 weeks, matched at 80% of the age-predicted maximal heart rate. ***Main Outcomes:*** The primary outcome was the Movement Disorders Society Unified Parkinson's Disease Rating Scale (UPDRS-II) score. Secondary outcomes were Parkinson's Disease Quastionnaire-39 (PDQ-39), the Beck Depression Inventory (BDI), the Schwab and England Activities of Daily Living (SE-ADL) scale, Euro-Quality of Life-5 Dimensions (EQ-5D) questionnaire, the Berg Balance Scale (BBS), the Balance Evaluation Systems Test (BESTest), the Tinetti Assessment Tool (TAT), the Dynamic Gait Index, the 6-min walk test (6MWT), and standing posturography. ***Results:*** After treatment, UPDRS-II scores improved (mean change: EXE, –4.5 points; CYC, –3.2 points). The results for the other outcomes (EXE and CYC, respectively) were: PDQ, 13 and 17%; BDI, –2.5 and –2.1 points; 6MWT, 129.6 and 141.6 m; and EQ-5D, 12 and 9% (all $p < 0.05$, but there was no difference between groups). EXE vs. CYC resulted in improved SE-ADL (8.4 and 4.0 points, effect size [ES]: 0.12), BBS (8.8 and 4.2 points, ES: 0.44), and 2 measures of posturography (ES: 0.11 and 0.21) ($p < 0.05$). BESTtest, TAT, the Dynamic Gait Index, and 4 out of 6 posturography measures did not change ($p > 0.05$). ***Conclusion:*** Two highly different exercise programs resulted in similar improvement of most motor and clinical symptoms in PD patients.

Introduction

Parkinson's disease (PD) affects mobility and balance and increases the risk of falls and compromises quality of life [1]. Exercise therapy could serve as an adjuvant to drugs and improve PD patients' mobility and clinical

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symptoms [2–4]. A variety of exercises have been advocated for improvement of PD patients' mobility and balance. Exercises not specific to patients' mobility dysfunction can also improve PD patients' mobility by a functionally meaningful margin. For example, exercise therapy using a treadmill [5–8], stationary cycling (CYC) [9, 10], and seated resistance training [11] with a low specificity for the temporal and spatial dynamics of standing and walking balance all improved PD patients' mobility, postural control, and balance. As demonstrated by a small effect size of 0.4 in a meta-analysis [3], the evidence is unclear with regard to the superiority of any specific exercise program in improving PD patients' mobility and balance. Accordingly, physical therapy in the form of balance, Tai Chi, dance, yoga, and walking training at different intensities and frequencies all improved PD patients' mobility and balance [3, 4].

The common element in these studies is that most PD patients have a low physical fitness. The unanswered question is whether exercise not specific to mobility impairments would also be effective in improving PD patients' walking and balance abilities. Based on the data in healthy old adults [12] and the similar effectiveness of many exercise programs in improving PD patients' mobility and clinical symptoms [3, 4], we expected to find no difference in effects on PD patients' clinical and mobility symptoms between the 2 interventions. The rational for this hypothesis is that "movement strategy"-based interventions [4] comprise, in addition to the symptom-specific components, a physical conditioning component, which would override the symptom-specific effects in PD patients with low levels of fitness. If this were the case, clinicians would have an evidence-based wider choice to prescribe exercise to improve PD patients' mobility. To test this hypothesis, we selected 2 vastly different exercise modalities: one which is rich in visual, acoustical, and proprioceptive stimuli, prompting patients to perform complex movements on surfaces of variable stiffness and one which is poor in such stimuli, performed in a seated position but still accepted as a rehabilitation modality for improving neurological patients' mobility. Though different in terms of the composition and nature of the stimulus, both programs are of an aerobic in nature and evidence based, resulting in a comparative effectiveness trial. The purpose of this randomized clinical trial was to directly compare the effects of 5-week-long agility exergaming (EXE) and CYC on PD patients' mobility and clinical symptoms.

Methods

Patients and Design

Patients with neurological symptoms visited a neurologist who conducted a neurological exam. With a likely diagnosis of PD, the neurologist ordered a structural MRI and an L-dopa test. If a patient responded to drugs positively, PD was diagnosed and the patient was entered into the hospital's database with the code for PD. Using consecutive sampling, we identified 88 PD patients in the database who met the initial inclusion criteria. Patients were asked to participate in this study and scheduled for two 1-h visits. Visit 1 comprised the Euro-Quality of Life-5 Dimensions (EQ-5D) questionnaire, the Movement Disorders Society Unified Parkinson's Disease Rating Scale (UPDRS-II), the Beck Depression Inventory (BDI), the Schwab and England Activities of Daily Living (SE-ADL) scale, posturography on a force platform, and Parkinson's Disease Questionnaire-39 (PDQ-39). Visit 2 comprised measurement of the Dynamic Gait Index (DGI), the 6-min walk test (6MWT), the Berg Balance Scale (BBS), the Tinetti Assessment Tool (TAT), and the Balance Evaluation Systems Test (BESTest). The same testing schedule was done after the intervention. Participants gave written informed consent to participate in this study, which was approved by the University Hospital's Ethics Committee. This trial is registered at Clinicaltrials.gov (NCT03193268) and has an ORCID ID (Tibor Hortobágyi: 0000-0002-5731-6423).

Inclusion criteria were: Hoehn and Yahr disease stage 2–3, UK Brain Bank criteria, being in neurologically and pharmacologically stable condition for a minimum of 6 months, and the presence of mobility, balance, and postural problems. Exclusion criteria were: a Mini Mental State Examination score <24, a Beck Depression Inventory score >40, severe cardiac disease (including congestive heart failure, ischemic disease, presence of a pacemaker, and orthostatic hypotension; 6 patients were excluded), uncontrolled diabetes, a history of stroke, traumatic brain injury, a seizure disorder, use of a deep brain stimulator (n = 3), ongoing orthopedic surgeries (n = 2),use of a pacemaker (n = 2), hemophilia (n = 1), clinically significant motor fluctuations and LD-induced dyskinesia, or current participation in a self-directed or formal group exercise program. In each patient, brain abnormalities were checked using a diagnostic MRI. Online supplement 1 shows the CONSORT flowchart (see www.karger.com/doi/10.1159/000493127 for all online suppl. material).

In a single-blind trial, patients (n = 74) were randomized into the following groups: EXE (n = 25), CYC (n = 25), or wait-list control (CON, n = 24). The principal investigator performed the randomization. He drew a colored ribbon from a covered box and attached one ribbon to each patient's folder (EXE: red, CYC: blue, and CON: green). After randomization, the patients participated in a practice session and were familiarized with each test, they received a detailed briefing about the program, and patients in the EXE group watched the EXE modules. The order of the motor tests was standardized among patients and testing sessions. Pretests and posttests were performed within 1 week of the intervention. Two physical therapists and a physical therapy assistant administering the tests were masked to the patients' group assignments. Every effort was made to keep patients in the EXE and CYC groups separate during the trial to minimize contamination: EXE and CYC patients had separate lockers and exercised in different rooms with independent entrances but at about the same time of day, i.e., 1–2 h after taking their medica-

tion in the morning. The interventions were conducted in three 5-week-long waves. We used CON to determine the effects of testing alone and the rate of disease progression over 5 weeks.

All patients remained "on" medication so that the assessments at baseline and after the intervention and each exercise session occurred 1–2 h after the patients took PD medications. Other than L-dopa drugs, patients took antihypertensive (EXE: $n = 12$, CYC: $n = 10$, and CON: $n = 8$), muscle relaxant (EXE: $n = 5$, CYC: $n = 8$, and CON: $n = 2$), and diabetes medications (EXE: $n = 1$, CYC: $n = 1$, and CON: $n = 2$). The patients' medications were not changed during the course of this study. There were 20 patients who were registered to use a cane but none of them used it or other assistive devices during the assessments or the intervention. None of the patients were enrolled into physical therapy for the 2 years preceding the start of this study, but 67 patients had received physical therapy 2 years earlier.

Outcome Measures

The primary outcome was the validated version of the UPDRS-II, which is sensitive to changes in a broad spectrum of PD symptoms [13] and measures clinically relevant hand, bed, mobility, and freezing-related experiences. A physical therapist, blinded to group allocation, read the questions and recorded patients' responses to the questions. The outcome was the absolute change score computed to reflect reductions (improvements) in symptoms.

Secondary outcomes addressed life domains and included change scores for: (1) SE-ADL; (2) EQ-5D, to measure 5 aspects of health-related quality of life; (3) PDQ-39, a quality-of-life questionnaire; (4) BDI; (5) TAT, a valid and reliable (intraclass correlation $R > 0.80$) test in PD to asses gait and balance [14]; (6) BESTest, a valid and reliable ($R > 0.90$) test to asses 6 domains of balance control [15]; (7) BBS, a valid and reliable ($R = 0.80$) test to assess fall risk [16]; (8) DGI, a valid and reliable ($R > 0.84$) tool to asses gait adaptability [17]; (9) the 6MWT, a valid and reliable ($R = 0.95$) index of walking capacity [18, 19], and (10) postural stability by the magnitude of center of pressure path in standing on a force platform (Posture Evaluation Platform; Med-Eval Co., Budapest, Hungary) in a wide, narrow, and tandem stance with eyes open or closed for 20 s after 1 familiarization trial in each condition [20]. Adverse events were not systematically assessed.

Interventions

The interventions consisted of twenty-five 1-h sessions over 5 weeks conducted in the hospital's outpatient physical therapy gym. Up to 3 physical therapists, who were trained and supervised by the principal investigator and who did not perform the assessments, delivered the interventions for groups of 4–8 patients at the same of time of day. The intervention was conducted in 3 waves over 15 weeks. A neurologist was on call. Heart rate was recorded in each patient and session to: (1) prevent patients from becoming ill due to the high exercise intensity and (2) match cardiovascular loads in EXE and CYC. Polar watches (Polar model RS800CX; Polar Electro Co. Ltd., Kempele, Finland) were strapped to the chest. The target heart rate was computed using the Karvonen formula, resulting in a heart rate range of 110–140 beats/minute, and these values were paired with an auditory warning beep. Borg's rate of perceived exertion (RPE) was measured. Each session started with a 5-min warm-up followed by 45-min of EXE or CYC and concluded with a 5-min cool down; 5 min of rest were included over the 60-min-long session [21].

EXE used the following 3 visual feedback modules of the Xbox 360 core system (Kinect Adventures video game; Microsoft Co., Redwood, WA, USA) for 15 min each: (1) Reflex Ridge, which prompts users to reflexively respond to visual stimuli; (2) Space Pop, which prompts performers to reach targets with the 4 extremities and the entire body to improve spatial orientation, and (3) Just Dance, which prompts users to generate and combine movement sequences [21]. Briefly, EXE was designed to improve postural control, gait mobility, gait stability, turning, and dynamic and static. Online supplement 2 shows a video clip of EXE.

CYC patients participated in a "spinning class." Patients sat on the seat of a bicycle ergometer and rode at 110–140 beats/min. RPE was also measured. Participants followed therapists' instructions to be within the target zone. CYC did not receive visual feedback but listened to music. Exercise was administered in 5-min-long bouts interspersed with 1 min of freewheeling. The purpose of CYC was to improve cardiovascular fitness and minimize the exercise stimulus for walking skills, dynamic and static balance, and turning skills.

Wait-listed CON continued with their habitual activity and were offered enrollment into supervised exercise after the study. All patients, including CON, were asked not to change their diet, medication, or exercise habits for the duration of this study.

Statistical Analyses

Using GPower statistical software, we estimated the number of participants needed for a significant group (EXE, CYC, and CON)-by-time (pre and post) interaction for the primary outcome UPDRS-II using a change of 4 points over 5 weeks of intervention (>3.1, functionally meaningful change) [13]. Using an α of 0.05, $1 - \beta$ (power) of 0.8, three groups, and a correlation of 0.5 between repeated measures, the total sample size needed was 67. Anticipating patients not meeting the inclusion criteria and dropouts, we randomized 74 patients.

Data are expressed as means ± SD. The variables were normally distributed based on the Shapiro-Wilk test. The main analysis was a group (independent variable: EXE, CYC, and CON) by δ score analysis of variance followed by Tukey's post-hoc contrast. We corrected for family-wise error by adjusting the p values for group-by-time interactions using the step-down Holm method by dividing the smallest of the 19 p values by 19, the next smallest p value by 18, and so forth. $p < 0.05$ was considered statistically significant. All statistical analyses were conducted with SPSS version 22.

Results

Baseline

Table 1 shows that, except for 3 variables, EXE and CYC did not differ at baseline.

CON did not change in any of the measures (all $p > 0.05$; Table 2). In EXE, 68 and 32% of patients took L-dopa and dopamine agonists. In CYC, 80 and 20% of the patients took L-dopa and dopamine agonists. In CON, 52 and 48% of the patients took L-dopa and dopamine agonists. Patients took other drugs in negligible quantities.

Table 1. Participant characteristics in the EXE, CYC, and CON groups at baseline

Variable	EXE (n = 25; 12 M)	CYC (n = 25; 11 M)	CON (n = 24; 13 M)	p
Age, years	70.0±4.69	70.6±4.10	67.5±4.28	0.036
Height, cm	173.0±6.91	173.8±6.11	174.7±7.48	0.955
Mass, kg	72.2±6.33	75.1±6.91	73.6±8.65	0.705
BMI	24.2±3.13	24.9±2.65	24.2±3.21	0.375
Time with PD, years	7.5±1.76	7.5±2.16	7.3±2.21	0.644
Hoehn and Yahr stage	2.3±0.48	2.4±0.51	2.4±0.51	0.632
L-dopa equivalent, mg/day	805.2±130.83	786.4±120.93	825.4±126.55	0.566
MDS-UPDRS M-EDL	18.2±3.85	18.9±3.11	19.0±4.67	0.750
Mean PDQ-39 score	6.4±1.14	6.5±1.61	7.0±1.67	0.925
Mobility subscore	16.2±5.98	17.2±6.80	16.8±5.51	0.856
BDI	12.4±2.75	12.7±3.24	12.4±2.94	0.587
SE ADL, %*	71.6±9.43	70.0±10.80	67.4±12.14	0.145
EQ-5D VAS, mm	64.9±9.68	62.8±10.90	68.5±9.10	0.259
EQ5 (sum of sub-items	14.4±1.41	13.9±2.26	13.4±2.13	0.403
BBS[1]	23.6±3.60	22.7±4.24	26.3±5.21	0.019
BESTest	71.5±12.35	72.1±10.43	73.0±12.63	0.910
TAT	17.9±2.03	17.6±2.14	17.3±2.60	0.677
Dynamic Gait Index[1]	16.3±0.99	16.6±1.23	16.4±1.24	0.764
6MWT, m	204.6±34.94	222.4±40.85	270.2±90.66	0.001
COP path, cm				
Wide stance				
EO	7.3±3.88	6.8±6.86	6.4±5.08	0.864
EC	5.5±1.47	6.1±2.77	7.3±2.57	0.669
Narrow stance				
EO	8.6±3.98	9.2±6.37	8.8±7.28	0.927
EC	10.3±4.22	9.5±5.00	11.0±4.02	0.519
Tandem stance				
EO	24.1±5.86	20.3±8.12	23.5±7.50	0.147
EC	25.2±8.53	23.6±9.76	26.2±11.76	0.655

Values are presented as means ± SD. EXE, 25 exercise sessions over 5 weeks using exergaming; CYC, 25 exercise sessions over 5 weeks using stationary cycling; CON, control (no exercise); M, males; PD, Parkinsons's disease; MDS-UPDRS M-EDL, Movement Disorders Society Unified Parkinson's Disease Rating; Scale Motor Experiences of Daily Living; PDQ-39, Parkinson's Disease Questionnaire-39; BDI, Beck depression inventory (0–20; lower values indicate less depression); SE-ADL, Schwab and England Activities of Daily Living Scale (PD) (0–100; 100 = no mobility disability). EQ-5D VAS, Euro-Quality of Life-5 Dimensions questionnaire visual analogue scale; BBS, Berg Balance Scale (0–20, high fall risk; 21-40, medium fall risk; 41-56, low fall risk). BESTest, Balance Evaluation Systems Test (maximal score: 108); TAT, Tinetti Assessment Tool (maximal score: 28, scores ≤19 indicate a high fall risk); 6MWT, 6-min walk test (higher values denote a better walking capacity); COP, center of pressure measured in quiet standing; EO, eyes open; EC, eyes closed.
[1] Maximal score: 24; scores <19 predict falls.

Exercise Intensity

There were no differences between EXE and CYC in RPE (EXE, 13.6 ± 1.25; CYC, 13.6 ± 0.88; p = 0.827) or exercise heart rate (EXE, 120.6 ± 1.75; CYC, 119.5 ± 1.82; p = 0.691), measured during 25 exercise sessions.

Primary Outcome

Changes in UPDRS-II did not differ ($p > 0.05$) between EXE (–23.9% ± 11.0) and CYC (–16.7% ± 12.36) but exceeded the –1.2% change in CON (group-by-time interaction, $F_{2,70} = 20.8$, $p = 0.001$).

Secondary Outcomes

The PDQ mobility subscore improved in EXE and CYC similarly and more than in CON (interaction, p = 0.001). The 2 interventions improved depression similarly (–17%, $p < 0.001$). EXE only improved SE-ADL by ~13% ($p < 0.05$). EQ5D-VAS improved similarly in EXE

Table 2. Changes in absolute units in the EXE, CYC, and CON groups

Variable	EXE (n = 25)	CYC (n = 25)	CON (n = 24)	$F_{2,71}$*	p*	$p\eta^2$	HSD	1 – β	Post-hoc comparisons
Mass, kg	–2.9±1.27	–4.4±1.66	0.2±1.13	69.5	0.001	0.67	0.79	1.00	All different
UPDRS–II	–4.5±2.45	–3.2±2.59	–0.1±2.19	20.8	0.001	0.39	1.30	1.00	CON vs. EXE, CYC
PDQ–39 mean score	0.5±1.06	0.5±0.71	1.1±0.58	4.9	0.010	0.12	0.45	0.77	CON vs. EXE, CYC
Mobility subscore	–2.9±3.37	–3.5±4.39	–0.4±1.16	5.9	0.004	0.15	1.91	0.88	CON vs. EXE, CYC
Beck depression index	–2.5±2.28	–2.1±2.35	0.1±1.98	9.8	0.001	0.20	1.27	0.97	CON vs. EXE, CYC
SE–ADL, %	8.4±6.88	4.0±6.45	2.2±8.50	4.7	0.012	0.12	4.16	0.79	CON vs. EXE
EQ5D VAS	6.6±7.74	4.4±9.05	0.4±5.82	3.9	0.024	0.10	4.09	0.71	CON vs. EXE, CYC**
EQ5D (sum)	–2.6±1.61	–2.0±2.14	0.1±1.44	15.1	0.001	0.29	1.01	0.99	CON vs. EXE, CYC
BBS	8.8±4.61	4.2±4.17	–1.4±5.91	25.7	0.001	0.44	2.82	1.00	All different
BESTest	3.2±5.60	5.1±9.46	–0.3±8.22	2.8	0.066	0.08	5.55	0.57	Not applicable
TAT	–5.0±13.79	–1.4±2.74	–0.2±1.59	2.3	0.111	0.06	5.19	0.46	Not applicable
Dynamic Gait Index[1]	0.7±1.77	0.3±0.98	–0.5±1.31	4.8	0.011	0.13	0.84	0.82	CON vs. EXE
6MWT, m	129.6±68.90	141.6±51.53	–16.3±81.61	39.4	0.001	0.53	12.3	1.00	CON vs. EXE, CYC
COP path, cm									
Wide stance									
EO	–4.5±4.11	–2.0±4.53	0.7±4.04	9.1	0.001	0.21	2.36	0.98	CON vs. EXE
EC	–2.0±2.37	–1.8±3.96	0.4±4.07	3.4	0.038	0.11	2.04	0.73	CON vs. EXE**
Narrow stance									
EO	–3.0±4.68	–3.8±6.16	–0.5±7.07	1.9	0.155	0.06	3.43	0.44	Not applicable
EC	–4.2±5.56	–3.9±5.51	–1.0±5.14	2.6	0.083	0.08	3.08	0.56	Not applicable
Tandem stance									
EO	–6.2±9.04	–3.1±6.78	–1.8±8.36	1.8	0.167	0.04	4.21	0.31	Not applicable
EC	–1.9±10.93	1.5±12.32	–1.4±13.33	0.5	0.573	0.02	3.33	0.14	Not applicable

Values are presented as means ± SD. EXE, 25 exercise sessions over 5 weeks using exergaming; CYC, 25 exercise sessions over 5 weeks using stationary cycling; CON, control (no exercise); M, males; PD, Parkinsons's disease; MDS-UPDRS M-EDL, Movement Disorders Society Unified Parkinson's Disease Rating; Scale Motor Experiences of Daily Living; PDQ-39, Parkinson's Disease Questionnaire-39; BDI, Beck depression inventory (0–20; lower values indicate less depression); SE-ADL, Schwab and England Activities of Daily Living Scale (PD) (0–100; 100 = no mobility disability). EQ-5D VAS, Euro-Quality of Life-5 Dimensions questionnaire visual analogue scale; BBS, Berg Balance Scale (0–20, high fall risk; 21-40, medium fall risk; 41-56, low fall risk). BESTest, Balance Evaluation Systems Test (maximal score: 108); TAT, Tinetti Assessment Tool (maximal score: 28, scores ≤19 indicate a high fall risk); 6MWT, 6-min walk test (higher values denote a better walking capacity); COP, center of pressure measured in quiet standing; EO, eyes open; EC, eyes closed. [1] Maximal score: 24; scores <19 predict falls. * Group (EXE, CYC, CON)-by-time (pre, post) interaction based on post- minus pregain scores. ** Did not survive Holm adjustment for multiple comparisons.

(11.7%) and CYC (8.9%) but the p value for this interaction did not survive the Holm adjustment for multiple comparisons. Also, the EQ5D sum improved similarly ($p > 0.05$) in EXE (18.0%) and CYC (13.0%, both $p < 0.05$). The distance in the 6MWT increased similarly ($p > 0.05$) in EXE (68.7%) and CYC (67.4%, both $p < 0.05$). BBS scores improved more ($p < 0.05$) in EXE (39.3%) than in CYC (21.3%, both $p < 0.05$). In 2 of the 6 center of pressure measures, the average improvements were greater ($p < 0.05$) in EXE (–3.3 cm) than in CYC (–1.9 cm) but the p value for one of these interactions did not survive the Holm adjustment for multiple comparisons. No other changes were significant (Table 2). Compliance was 100%, the dropout rate was 0%, and there were no adverse events.

Discussion

The purpose of this randomized comparative effectiveness trial was to directly compare the effects of 5-week-long EXE and CYC on PD patients' mobility and clinical symptoms. As hypothesized, we found small differences in the effects produced by agility and cycling training on PD patients' motor and clinical symptoms. Matched for cardiovascular load and perceived effort, EXE and CYC had similar improvements in the primary outcome, i.e., UPDRS-II (~24 and ~17%). The data provide evidence for the presence of a general exercise effect on PD patients. We discuss the findings with a perspective on how physical conditioning (fitness) might be a common factor among the many types of exercise programs that improve PD patients' mobility and clinical symptoms.

Primary Outcome

The 2 interventions resulted in similar improvements in UPDRS-II, i.e., 4.5 (EXE) and 3.2 (CYC) points, exceeding the minimal clinically important difference of 3.1 points (Table 2) [13]. The improvement in 31 of the 50 exercising patients exceeded the 3.1 threshold. The UPDRS-II quantifies self-reported oral, hygienic, hand, bed, walking mobility, and freezing-related experiences with sensitivity to changes in both functions and dysfunctions across a range of PD stages and years [13, 22]. The improved perception of daily functions was probably due to a physical conditioning effect. This is plausible because EXE comprised high variations in sensory and motor skill stimuli, while CYC had no variation in the motor skill stimulus. However, the 2 programs were completed with the same effort as measured by heart rate and perceived exertion. We speculate that patients needed to make less of an effort after versus before training, to perform ADL tasks, resulting in functionally meaningful changes in UPDRS-II scores. It is also possible that intensive exercise improved cognition, including executive function, which is known to mediate the role of fitness in determining daily function in healthy old adults [23].

Secondary Outcomes

We observed a change of only 0.5 points in the PDQ-39 but meaningful changes of 4.4–6.6 points in the EQ5-VAS. Perhaps perceived mobility drove improvements in QoL because the 2 interventions improved the mobility element of the PDQ-39 and the SE-ADL similarly by ~7–17% (Table 2). The depression scores improved but did not move our patients to the "mild" category from the "moderate" depression category (Table 2). Weight loss did not affect the clinical outcomes unfavorably in EXE or CYC (Table 2). Rreduced weight could help PD patients to perform lower-extremity movements with a larger range of motion and improve mobility.

The 204- to 270-m distance in the 6MWT at baseline (Table 1) is far below the norm (499 m) reported for healthy old adults aged 70–79 years [24] and the 392 m reported in a large PD cohort [25]. These values suggest low walking and dynamic balance abilities and fitness and a high potential for improvements. The 129.6- and 141.6-m increases in the 6MWT distance (both $p < 0.05$; Table 2) suggest improvements in fitness and walking and balance abilities far exceeding the ~5 m increase in the ParkFit study [25]. Especially in low-fitness individuals, such as our patients, the walking distance at baseline [26] and the increases in the distance walked correlate with the maximal oxygen uptake up to $r = 0.77$ [27–30] (a measure of cardiorespiratory fitness), suggesting that EXE and CYC could improve PD patients' walking and balance abilities due to increased physical conditioning and fitness.

Our patients' baseline BBS scores of 23–26 (Table 1) were well below the age-based norms [24], suggesting the presence of a dysfunctional balance. The greater improvements in BBS after EXE (39%) compared with CYC (21%) (Table 2) suggest that EXE compared to CYC was more specific in correcting less and also more difficult balance problems. Unlike for the 6MWT, increases in fitness may not be effective or specific enough to correct balance problems in stage 2–3 PD patients. The balance-specific changes caused by EXE in BBS scores were, however, not confirmed by changes in other measures of balance because the changes did not favor EXE versus CYC in the BESTest, the TAT, the DGI, and 4 measures of standing balance (Table 2).

Generality of Exercise Effects on PD symptoms

Our patients' mobility improved independent of exercise type. A synthesis of previous data is consistent with a physical fitness effect. Treadmill [6–8], CYC [9, 10], and seated resistance training [11], with a low or no specificity to the temporal and spatial dynamics of standing and walking postures and balance, all improved PD patients' mobility and balance as well or even more effectively than did balance, Tai Chi, dance, yoga, and walking training [3]. As in the present experiment, the patients in these studies were physically untrained and high-intensity and high-frequency exercise is particularly effective in improving motor performance [2]. Overall, the generality of exercise effects observed in the present study agree with the conclusion of a recent consensus statement concerning the efficacy of a broad range of physical therapy and "movement strategy"-based interventions [4]. Physical fitness is associated with improvements in the sense of fatigue, standing and walking balance, and the level of perceived effort relative to the maximal available capacity to execute ADL tasks.

Quantifying exercise intensity during agility and balance training is difficult. It is best captured by the "tasks being well within the balance capability of the individual to perception of the challenges as being at the limits of balance capabilities" [p. 10 in 31]. Several studies reported "high-intensity" exercise training in PD patients without quantifying the intensity of balance, walking, dance, yoga, or Tai Chi training [2, 3, 32]. By controlling exercise intensity via heart rate and RPE in the present study, the efficacy of different exercises could be compared. Because participants in EXE and CYC exercised at ~120 beats/min or an RPE of 12–13, the exercise intensity was high and com-

parable in the 2 intervention groups, a direct comparison not done before.

Our data support the choice of EXE for the treatment of PD patients' postural dysfunction. EXE can be used to dose and individualize the exercise stimulus, delivered in an entertaining and competitive manner by having patients teamed up against each other (present study). In addition, patients become intrinsically motivated and perceive physical exertion as less demanding and of a lower intensity than other exercises not embedded in a gaming or virtual environment [33–36]. Presumably the weight shift and other postural manipulations reduce postural dysfunction by improving muscle activation, the rate of tension development, and other neuromuscular functions [37]. Still, our data for the first time suggest that when the intensity of exercise is matched between EXE and CYC most of the PD symptoms improve similarly (Table 2) [38]. The present data help to reduce the uncertainty concerning the efficacy of technology-aided exercise interventions in PD, as a recent review concluded that "…there is 'insufficient evidence' for technology-based movement strategies, and the implication for clinical practice is 'investigational' when interventions using Nintendo Wii, smartphone biofeedback, and a gamepad-'dancing software,' and in-shoe vibratory devices were considered" [4].

Limitations

One limitation of this study is its short duration. However, a 6-month-long treadmill intervention with exactly the same intensity as EXE and CYC did not produce time-proportionally larger effects [8]. Exercise effects are often not sustained in PD patients [34] and we cannot tell whether the program slowed disease progression. We note that the PD symptoms of the CON did not get worse over 5 weeks. Executive function, a variable we did not measure, can act as a moderator of improvements in mobility [23]. Patients could have modified their physical activity and diet during the study period, affecting the results, but we did not measure these factors. While the 100% adherence and 0% dropout rates make a high exercise intensity feasible [8], therapists delivered exercise sessions in a designated hospital facility, conditions often unavailable to PD patients. However, patients could perform agility exercises or cycle on an ergometer at home with remote supervision, reducing costs and staff burdens [26, 35]. In this randomized comparative effectiveness trial the assessors were blinded to the patients' group assignment; there could still be a bias in the assessments because there was no assessment of masking maintenance. Without neural, biomechanical, or behavioral markers, we were unable to determine if EXE and CYC produced the mobility and clinical effects through different mechanisms.

Conclusions

Five-week-long EXE and CYC ergometer exercise programs at an RPE of 12–13 improved most of the motor and clinical symptoms similarly in PD patients. An increase in fitness may underlie the favorable effects produced by highly diverse exercise programs on motor and clinical symptoms of PD patients who are physically deconditioned at baseline. Clinicians can prescribe CYC in addition to EXE to improve stage 2–3 PD patients' mobility and clinical symptoms.

Disclosure Statement

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Highlights

- Many motor interventions can improve PD patients' clinical status.
- Direct comparisons between interventions are lacking.
- Patients exercised at the same cardiovascular load while performing EXE or CYC.
- The 2 interventions improved the primary outcome similarly by 3.2–4.5 points
- The distance walked in 6 min, a measure of fitness and walking ability, improved similarly.
- Increases in the BBS were greater after EXE than after CYC.
- Motor and nonmotor symptoms improved independently of the exercise stimulus.

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