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ORIGINAL RESEARCH

Comparative Effectiveness of 4 Exercise Interventions Followed by 2 Years of Exercise Maintenance in Multiple Sclerosis: A Randomized Controlled Trial

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Abstract

Objective: To determine the effects of exergaming (EXE) on quality of life (QOL), motor, and clinical symptoms in multiple sclerosis (MS). We compared the effects of EXE, balance (BAL), cycling (CYC), proprioceptive neuromuscular facilitation (PNF), and a standard care wait-listed control group on clinical and motor symptoms and quality of life (QOL) in people with MS (PwMS) and determined the effects of subsequent maintenance programs for 2 years in a hospital setting.

Design: A randomized controlled trial, using before-after test design.

Setting: University hospital setting.

Participants: Of 82 outpatients with MS, 70 were randomized (N=70), and 68 completed the study.

Interventions: The initial high-intensity and high-frequency interventions consisted of 25 one-hour sessions over 5 weeks. After the 5-week-long initial intervention, the 2-year-long maintenance programs followed, consisting of 3 sessions per week, each for 1 hour.

Main Outcome Measures: The primary outcome: Multiple Sclerosis Impact Scale (MSIS-29). Secondary outcomes: Measures 5 aspects of health-related QOL (EuroQol 5-Dimension questionnaire), Beck Depression Inventory, 6-minute walk test (6MWT), Berg Balance Scale (BBS), Tinetti Assessment Tool (TAT), and static BAL (center of pressure).

Results: MSIS-29 improved most in EXE (11 points), BAL (6), and CYC (6) (all $P<.05$). QOL improved most in EXE (3 points), CYC, and BAL (2) (all $P<.05$). TAT and BBS improved significantly ($P<.05$) but similarly ($P>.05$) in EXE, BAL, and CYC. 6MWT improved most in EXE (57m), BAL (32m), and CYC (19m) (all $P<.001$). Standing sway did not change. Maintenance programs further increased the initial exercise-induced gains, robustly in EXE.

Conclusions: A total of 25 sessions of EXE, BAL, CYC, and PNF, in this order, improved clinical and motor symptoms and QOL, and subsequent 2-year-long thrice weekly maintenance programs further slowed symptom worsening and improved QOL. EXE was the most and PNF was the least effective to improve clinical symptoms, motor function, and QOL in PwMS.

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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. Chronic inflammation causes a loss of neurons, myelination, physical and cognitive function, and quality of life (QOL), mostly in women aged 20-50 years.[1] Classical treatments of MS did not incentivize people with multiple sclerosis (PwMS) to engage in physical activity.[2-6] As a result of a recent paradigm shift, PwMS now participate in treadmill, arm and leg cycling (CYC), rowing, resistance, aquatic, calisthenics, balance (BAL), dance, yoga, and exergaming (EXE) training at times with robot assistance.[6-9] Data from animal models of MS, human imaging, and brain stimulation studies link the symptom-modifying or even disease-modifying effects of exercise to improvements in motor-cognitive function, synaptic plasticity, and promyelinating and immunomodulatory processes in disease-affected brain areas.[2-5]

While exercise is becoming an adjuvant to drug therapy of PwMS, key characteristics of exercise therapy remain scantly examined. The exercise-induced effects can be also inconsistent. The duration of exercise programs normally is a just a few weeks,[6,8,9] and even when programs last 6-9 months, QOL, fatigue, and autonomic nervous system functions may change little[10-12]; the small postexercise functional gains are rarely retained[7] or may even reverse to levels below pre-exercise baseline.[13] These data suggest the need to examine the hypothesis: if a long-term maintenance exercise program could be delivered, such a program could sustain or perhaps even potentiate the initial gains afforded by a high-intensity exercise program in PwMS.[14]

Not only are most MS exercise trials short, the scarcity of long-term comparative exercise trials, while urgently called for,[15-17] are lacking. The emerging picture from the few comparative effectiveness randomized trials reveals a lack of specificity, large interindividual variations in the responses to the exercise stimulus, and a low efficacy of certain type of exercise interventions.[18-24] While high-intensity exercise is strongly promoted in the hope that the ensuing functional improvements and neuroplasticity would scale with stimulus intensity without exacerbating symptoms,[2-5] such long-term comparative effectiveness studies are currently lacking in PwMS.[6,9] Conventional therapies were often based on Bobath-guided principles of proprioceptive neuromuscular facilitation (PNF) for improving spasticity, pain, muscle strength, and range of motion in PwMS. However, PNF's comparative effectiveness has been rarely studied in PwMS, and its efficacy on its own and in comparison with other treatments remains unclear.[25] Comparative effectiveness and the long-term effects of EXE, a relatively new therapy, has been rarely examined in PwMS.[9,26] Unlike most other exercise modalities such as CYC or even BAL training, in which the exercise stimulus tends to plateau over time, EXE increases difficulty of a given task incrementally from one trial to the next based on immediate feedback, motivation, and reward in real time, and it affords rich, complex, and cardiovascularly demanding stimuli to reduce sensorimotor dysfunctions in PwMS.[27] Because of these properties and because of its high efficacy in PwMS, people with Parkinson disease, people with stroke, and older adults in our previous studies,[27-31] we hypothesized that EXE will improve clinical and motor symptoms more effectively than BAL and CYC training compared with an active PNF and a no-intervention control group. The purpose of the present study was to compare for the first time the effects of 5-week-long high-intensity and high-frequency (5 sessions/wk) sensorimotor-enriched EXE, BAL, and CYC exercise training with PNF and control group on clinical and motor symptoms and QOL in PwMS. We also examined if a 2-year-long thrice weekly EXE, BAL, CYC, and PNF maintenance programs would potentiate the effects of initial high-intensity and high-frequency exercise programs.

List of abbreviations:

BAL	**balance**
BBS	**Berg Balance Scale**
CYC	**cycling**
EQ-5D	**EuroQol 5-Dimension questionnaire**
EXE	**exergaming**
MS	**multiple sclerosis**
MSIS-29	**Multiple Sclerosis Impact Scale**
PNF	**proprioceptive neuromuscular facilitation**
PwMS	**people with multiple sclerosis**
$p\eta^2$	**partial eta squared**
6MWT	**6-minute walk test**
TAT	**Tinetti Assessment Tool**

Methods

Design and participants

This is an assessor-blinded, 4-intervention, comparative effectiveness, randomized controlled trial with measurements before and immediately after the 5-week-long high-intensity and high-frequency interventions, with additional measurements at 6, 12, 18, and 24 months during maintenance programs (fig 1). The hospital's chief neurologist confirmed the diagnosis of MS, rated MS severity by Expanded Disability Status Scale, and briefed participants about study aims, who were then were tested for cognitive function by a neuropsychologist and signed a consent form. A therapist not involved in the trial performed the concealed randomization of 70 PwMS into the 5 groups: high-intensity EXE (n=14,12 female), high-intensity BAL (n=14,12 female), high-intensity CYC (n=14, 13 female), active PNF control (n=14,13 female), and a standard care, wait-listed, no-intervention control group (control, n=12,11 female) (see fig 1).

Inclusion criteria were either sex, aged 30 years or older, Expanded Disability Status Scale score of 4-6, relapse frequency ≤1/y over the past 5 years to minimize a change in medication, and Mini-Mental State Examination score ≥20. Exclusion criteria were steroid therapy currently or during the past month, acute exacerbation of MS within 3 months of starting the program, radiological change in disease progression over the past 2 years, a substantial change in medication over the past year, use of a cane or walker, depression (Beck Depression Inventory score >40), a serious unstable medical condition, severe cardiac disease, hypotension, uncontrolled diabetes, history of stroke, traumatic brain injury, an epileptic seizure within a year, or current participation in a self-directed or formal exercise program.

Before the trial all participants and during the trial no participants but the control group were enrolled in standard physical therapy provided by government insurance for 30 minutes 2 × / wk. The Institutional Research Ethics Committee approved (IKEB2017/08) the registered (NCT04550650) study protocol.

Outcomes

Changes in the primary and secondary outcomes were measured before and after interventions and during the follow-ups by the

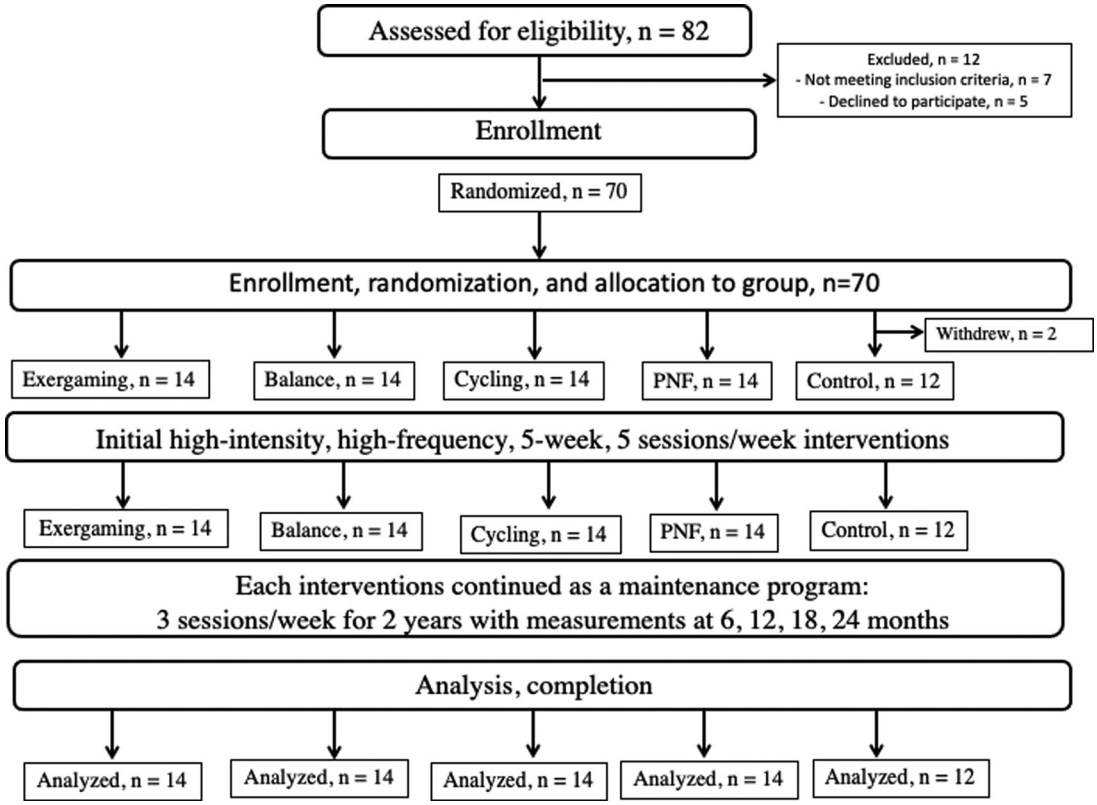

Fig 1 Flowchart.

same assessors, blinded to intervention allocation. Testing order was standardized among patients and testing sessions. Pretest and posttest were performed within 1 week of the interventions with a 48-hour gap between pretesting and Session 1 and between Session 25 and posttesting. Primary outcome was the Multiple Sclerosis Impact Scale (MSIS-29), a valid, reliable, and treatment-responsive measure of physical and psychological function in PwMS.[32,33]

Secondary outcomes addressed life domains and are valid and reliable in PwMS (R: 0.80-0.95). The EuroQol 5-Dimension questionnaire (EQ-5D) measures health-related QOL.[34] The Beck Depression Inventory quantifies depression.[35] The Tinetti Assessment Tool (TAT) measures gait and BAL.[36] The Berg Balance Scale (BBS) quantifies BAL, bodily coordination, and fall risk.[37] The 6-minute walk (6MWT) test measures walking capacity and fatigue.[38] Center of pressure path measures postural control while standing on a force platform (Posture 94 Evaluation Platform[a]) in a wide and narrow stance with eyes open and closed for 20 seconds after 1 familiarization trial per condition.[39]

Interventions and maintenance programs

The interventions aimed to improve clinical and motor symptoms of MS, QOL, postural stability, and mobility. Participants were familiarized with the tests and the exercises. Groups of 4-6 patients exercised in 1 of 3 outpatient gyms concurrently throughout the day, but a given patient exercised at the same time of the day (±1 hour).

The initial high-intensity and high-frequency interventions consisted of 25 one-hour sessions over 5 weeks. Up to 3 physical therapists, who were trained and supervised by the principal investigator and who did not perform the assessments, delivered the interventions. After each session, PwMS recorded their symptoms and therapists checked these diaries daily. Supplemental S1 details the 10-minute warm-up, the 40-minute interventions, and the 10-minute cooldown. EXE received sensorimotor and visuomotor agility training using 3 modules of the Xbox 360 core system (Kinect Adventures video game[b]). BAL performed dynamic and static BAL and stepping exercises in multiple directions. CYC was a spinning class. The intensity during EXE, BAL, and CYC corresponded to ~75% of age-predicted maximal heart rate and the rate of perceived exertion was 7 of 10 (PNF: 100 beats/min, rate of perceived exertion: 3/10).[27] A PNF-trained physical therapist delivered the PNF intervention. After the 5-week-long initial intervention, the 2-year-long maintenance programs followed, consisting of 3 sessions per week, each for 1 hour. The groups continued to perform their initially assigned exercise program. The control group was offered enrollment into supervised exercise after the study. All PwMS were asked not to change their diet, medication (including vitamin D dose), or exercise habits for the duration of this study.

Statistical analyses

We estimated the number of participants needed for a significant group (EXE, BAL, CYC, PNF, control group) × time (pre, post) interaction for the primary outcome.[40] A priori power analysis revealed that enrolling 12 PwMS/group with a 10-point[41] improvement in MSIS-29 relative to no change in the control group would produce a medium effect of 0.5 (α=0.05, power=0.8). We randomized n=70 PwMS in anticipation of dropout because of illness, adherence, and disease exacerbation.

Data are expressed as mean ± SD. Continuous variables were normally distributed based on the Shapiro-Wilk test. We compared the 5 groups at baseline using a 1-way analysis of variance or a Kruskal-Wallis test. We compared the gain score for continuous variables between the 5 groups using a 1-way analysis of variance or a Kruskal-Wallis text for categorical data. A significant effect, characterized by partial eta squared ($p\eta^2$) effect size, was interpreted as a group by time interaction and was followed by a Tukey's post hoc or a Mann-Whitney test to determine the means that were different. Cutoffs for $p\eta^2$ are ≥0.01 (small), ≥0.06 (medium), and ≥0.14 (large).[42] We further quantified the within group changes by Cohen effect size *d* (small=0.20; moderate=0.50; large=0.80). The Holm method was used to correct for family-wise error. We determined the relationship between changes in selected variables using Pearson product moment correlations. Conditional process mediation (Process macro; 5000 bootstrap samples, bias-corrected confidence intervals) determined if changes in variables mediated the effects of EXE, BAL, CYC, and PNF vs control group on MSIS-29. The level of significance was set at $P<.05$ (SPSS 22.0[c]).

Results

The 5 groups were similar at baseline (tables 1 and 2). Of the 70 patients (90% female), 62% had relapsing-remitting MS.

Effects of 5 weeks of initial exercise training and 2 years of maintenance on outcomes primary outcome

The initial 5-week EXE improved MSIS-29 by 10% (11 points, d=2.88), more ($P<.001$) than the 6% (6 points, $P<.001$) improvements in BAL (d=1.44) and CYC (d=1.61) (group × time interaction, F=35.1, $p\eta^2$=0.693, P=.001) without changes in PNF and control group. During the maintenance phase, the initial 10-point improvement further increased by 15 points (23%, d=6.33, $P<.001$) in EXE, while BAL and CYC returned to near baseline. At 24 months, all groups had better MSIS-29 scores than the control group ($P<.001$, d=1.13-5.62), and EXE had better scores than BAL, CYC, and PNF ($P<.001$, ~d=2.51). At 24 months, EXE's score was ~40 points better than the control group (figs 2

Table 1 Patient characteristics at baseline

Characteristic	EXE	BAL	CYC	PNF	Control	All
PPMS (RRMS), n	14 (7.7)	14 (5.9)	14 (5.9)	14 (5.9)	12 (4.8)	68 (26.42)
Female (%)	86	86	93	93	92	90
EDSS (median)	5.0	5.0	5.0	5.0	5.0	5.0
EDSS (range)	5-6	5-6	5-6	5-6	5-6	5-6
MSIS-29	108.7±9.29	110.7±9.76	106.0±10.35	110.1±8.59	109.8±10.67	108.8±9.57
MS duration (y)	12.1±2.68	13.6±4.07	13.2±4.42	12.7±4.25	14.0±4.11	13.1±3.89
Age (y)	48.2±5.48	46.9±6.46	48.1±5.65	46.9±5.57	44.4±6.76	47.0±5.95
Height (cm)	171.6±5.94	170.1±2.80	169.5±4.67	168.7±5.36	173.5±6.27	170.6±5.23
Mass (kg)	59.7±9.72	59.8±9.67	55.6±5.27	58.4±8.54	57.9±7.77	58.3±8.27
BMI	20.2±2.77	20.7±3.57	19.4±1.72	20.5±2.44	19.2±1.87	20.0±2.57
MMSE	27.2±1.05	26.9±1.23	27.2±1.05	26.7±1.54	26.8±1.11	27.0±1.20
Smoking, n (%)	3 (21)	7 (50)	4 (29)	6 (43)	3 (25)	23 (34)
Alcohol, 1-3 drinks/d, n (%)	7 (50)	10 (71)	6 (43)	6 (43)	6 (50)	35 (51)
Comorbidities (n)						
Thyroid dysfunction	4	4	3	3	5	19
Hypertension	4	5	4	2	0	15
Depression	2	1	5	1	3	12
Gastric inflammation	1	2	1	3	2	9
Rheumatoid arthritis	2	1	2	1	1	7
Epilepsy	0	0	2	2	2	6
Cardiac ischemia	2	1	1	1	0	5
Fibromyalgia	0	1	1	1	2	5
Anxiety	1	1	0	1	1	4
Vertebral hernia	0	1	1	2	0	4
Bipolar disorder	0	1	0	1	1	3
Diabetes	1	0	0	0	0	1
Drugs (n)						
Glatiramer acetate	5	7	5	8	5	30
Dimethyl fumarate	5	3	6	4	2	20
Natalizumab	4	4	3	2	5	18
Vitamin D, n (%)	11 (79)	12 (86)	11 (79)	10 (71)	11 (92)	68 (81)
IU/d	1519	1262	1286	1357	688	1221
IU/d (median)	857	929	1000	1143	857	857

NOTE. Values are mean ± SD unless otherwise indicated.
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EDSS, Expanded Disability Status Scale; MMSE, Mini-Mental State Examination; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Table 2 Secondary outcomes at baseline

Outcome	EXE	BAL	CYC	PNF	Control	F	*P* Value
EQ-5-VAS (mm)	62.1±6.99	64.3±6.46	61.4±6.63	62.9±6.11	64.2±5.15	0.5	.717
EQ-5-Sum score	13.9±2.18	13.6±0.93	13.4±1.83	13.9±1.44	13.3±0.89	0.3	.829
BDI	12.4±2.31	11.6±2.56	13.6±3.43	12.3±2.55	14.3±3.22	1.6	.185
TAT	15.9±1.86	16.4±1.22	15.7±1.98	16.4±1.22	16.7±1.61	0.8	.525
BBS	21.7±3.56	21.9±2.32	20.7±3.79	21.1±1.51	22.5±4.38	0.6	.674
6MWT (m)	235.8±35.48	230.4±30.03	245.7±41.08	244.3±52.98	243.3±39.56	0.4	.834
COP (cm)							
WEO	12.3±5.32	13.0±4.15	11.8±3.81	11.4±3.22	13.0±4.51	0.4	.817
WEC	8.6±3.61	9.3±2.98	7.8±2.70	8.7±2.23	8.9±3.60	0.5	.747
NEO	11.6±8.18	11.8±8.18	11.6±3.86	9.2±6.23	10.3±7.53	0.4	.828
NEC	12.0±3.86	11.7±3.31	11.4±5.03	10.4±3.01	10.1±3.79	0.6	.691

NOTE. Values are mean ± SD unless otherwise indicated. F and *P* values are for 1-way analysis of variance. BBS fall risk: 0-20: high, 21-40: medium, 41-56: low; 6MWT higher values denote better walking capacity, fitness; TAT maximal score 28, ≤19 high fall risk;
Abbreviations: BDI, Beck Depression Inventory (0-13: minimal; 14-19: mild; 20-28: moderate; 29-63: severe); COP, center of pressure measured in quiet standing for 20 s; NEC, narrow stance eyes closed; NEO, narrow stance eyes open; WEC, wide stance eyes closed; WEO, wide stance eyes open; VAS, visual analog scale.

and 3, supplemental S2, available online only at http://www.archives-pmr.org/).

Secondary outcomes

The initial 5-week intervention-induced improvements in EQ-5D were similar in EXE (3 points, 21%, d=2.41) and CYC (1.9 points, 13%, d=0.92, both $P \leq .023$), exceeding the changes in the other groups (∼1point, 1% to −7%, $P>.05$). The maintenance programs did not sustain or further increase these initial gains. At 24 months, the 4 groups had better scores than the control group ($P<.001$, d=0.44-4.99), and EXE had better scores than BAL, CYC, and PNF ($P<.001$, ∼d=1.84). At 24 months, EXE's score was ∼7 points better than the control group (see figs 2 and 3).

The initial 5-week program improved TAT similarly in EXE, BAL, and CYC (1.7-3.1 points, 11%-21%, d=0.79-1.77, all $P<.001$) compared with no changes in PNF and the control group (group × time interaction, F=8.3, $p\eta^2$=0.445, P=.001). Only the EXE maintenance program sustained but did not further improve gains in TAT. At 24 months, EXE had 3.4-7.5 points superior ($P<.001$, d=1.11-2.32) score than the other 4 groups.

The initial 5-week intervention-induced improvements in BBS were similar in EXE (6.1 points, 30%, d=3.43) and BAL (4.6 points, 23%, d=1.72, both $P<.001$), exceeding the 3.9- (13%, d=0.88), 2.5- (8%, d=0.46), and −0.2- (−0.3%, d=0.07) point changes, respectively, in CYC, PNF, and control group (group × time interaction, F=14.9, $p\eta^2$=0.487, $P<.001$). At 24 months, there was a difference of 12 points (d=6.98, $P<.001$) between EXE and the control group (see fig 2C).

The initial 5-week intervention-induced improvements in the 6MWT were 57 m (26%, d=3.99) in EXE, 32 m (15%, d=2.18) in CYC, and 19 m (10%, d=0.88) in BAL (all $P<.001$, all different $P<.001$, group × time interaction, F=7.3, $p\eta^2$=0.333, $P<.001$), exceeding the 5-m (4%) change in PNF and the control group. Only the EXE maintenance program improved the initial gains further by 21 m (d=3.33, $P<.001$), while BAL and CYC maintained the initial gains. At 24 months, PNF and the control group walked 21 m and 65 m shorter than baseline (both $P<.001$). At 24 months, EXE vs the control group walked 98 m farther (see fig 2D).

Measures of sway and depression did not change. At the individual level, we found no associations between changes in the primary outcome and changes in secondary outcomes (all $P>.05$), making conditional process mediation irrelevant.

Discussion

As hypothesized, EXE potentiated the effects of the initial exercise program in most outcomes during 2 years of EXE maintenance, and BAL, CYC, and PNF maintenance also slowed symptom worsening and improved QOL compared with the control group. EXE was the most effective and PNF was the least effective to improve clinical symptoms, motor function, and QOL in PwMS.

We set MSIS-29 score as the primary outcome, following recommendations for using a clearly defined clinical primary outcome in PwMS.[17] EXE improved MSIS-29 scores 3 points more than the 8-point clinically meaningful, minimal change (see figs 2 and 3, supplemental S2).[41] An effective intervention is expected to improve MSIS-29 scores by 8 points in 80% of PwMS (Expanded Disability Status Scale: ∼5). This was the case in EXE in the present study (11/14 patients improved ≥7 points) (see fig 3). The efficacy of EXE is highlighted by BAL and CYC improving MSIS-29 scores by ∼6 points less than EXE and ∼6 more than the 2 control groups. The improved MSIS-29 scores reflect that PwMS perceived themselves more capable to walk, BAL, and manipulate objects and felt an amelioration in clumsiness, stiffness, spasms, tremor, limb heaviness, and dependence on others. Only a few studies have assessed the effects of exercise training on MSIS-29.[17] Physical therapy, yoga, fitness and in-home EXE improved subscales of MSIS-29 relative to controls by ∼12%,[43,44] similar to the ∼10% in the present study (see figs 2A and 3A). However, other EXE or innovative BAL and gait interventions did not measure clinical outcomes.[13,15,16,18,23,24,45] Our data do not support the use of PNF to reduce spasticity and pain in PwMS.[25,46] (see fig 2)

EXE and CYC also improved health-related QOL (see fig 2B). This finding agrees with the favorable effects of a variety of motor interventions on QOL in PwMS[15,16,45,47] but disagrees with the nil effects reported previously.[17,48] EXE in particular was thus effective in improving both health- and disease-related QOL.

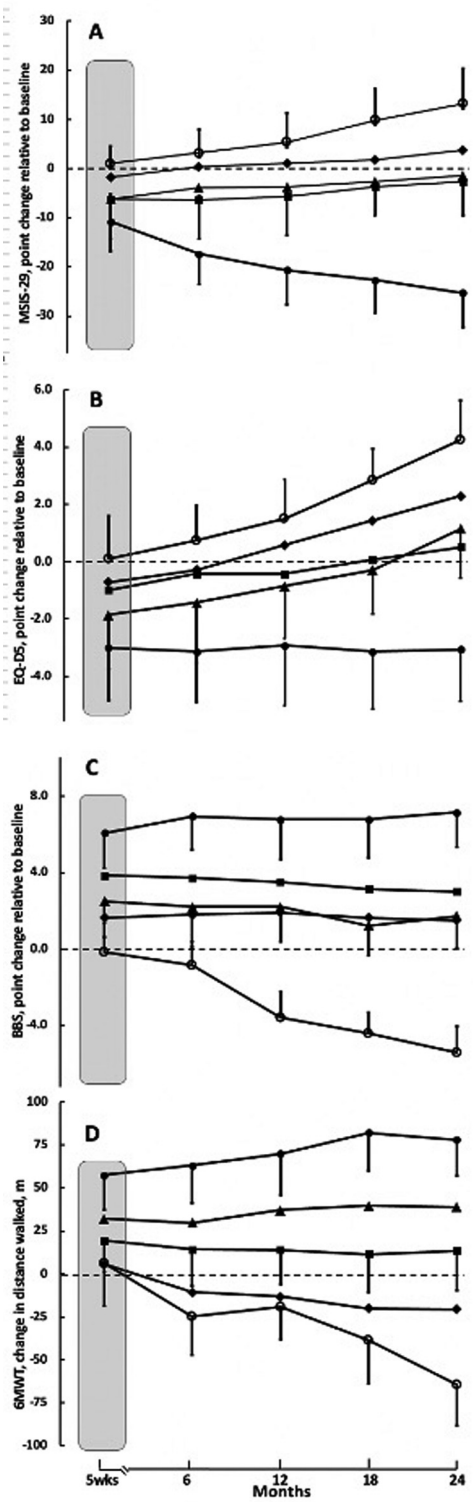

Fig 2 Change scores in outcomes. (A) MSIS-29; (B) EQ-5D; (C) BBS; and (D) 6MWT. In each panel, the group effect was significant on the gain scores, implying a group by time interaction. The shaded area denotes the change score computed as after minus before the 5-wk-long initial high-intensity and high-frequency interventions. BAL, filled squares; Control, open circles; CYC, filled triangles; EXE, filled circles; PNF, filled diamonds. Values below horizontal dashed line denote improvements in panels A and B. Horizontal dashed line denotes no change in outcomes relative to baseline. The text details the group by time interaction, which were significant in each panel.

Increases in fitness, mobility, and BAL might underlie improvements in QOL. Indeed, increases in TAT and BBS suggest improved dynamic and static BAL and perceived fall risk (see figs 2 and 3, supplemental S2).[47,49,50] The 57-m (EXE), 32-m (CYC), and 19-m (BAL) increases in walking ability are especially encouraging because of all clinical symptoms, walking ability becomes most impaired during 10 years of MS,[51] and slow gait can identify MS-specific dismobility beyond natural aging.[52] Walking ability is also related to fitness, which in turn reduces the sense of fatigue.[53] The superior efficacy of EXE compared with BAL, CYC, and PNF may rests in the complex sensorimotor stimulus, which can simultaneously address multifaceted dysfunctions of MS, including BAL, fall risk, postural control, and fitness.[16]

Study limitations

One limitation is that we have no data to determine if the interventions slowed the progression of the disease. It is still remains unclear for how long after the maintenance program the effects would last and if PwMS could continue the program on their own with minimal supervision.[6,7,9] We did not measure changes fatigue and cognition, important features of MS. We did not control for the social effects of small group exercise vs the control group not receiving social attention. We are unable to resolve the inconsistency in the data that while symptoms of depression improved when measured as a part of MSIS-29 and EQ5, Beck Depression Inventory did not change, which is in contrast to previous data.[24] Several trained therapists delivered and supervised the program in a hospital gym, conditions that are not feasible in other settings and are also against recent trends of telerehabilitation.[6,45] We did not monitor patients' diet and physical activity, which could affect the results. The assessors were blinded to patients' group assignment but we cannot tell if the masking was successfully maintained. We did not match specific elements of exercise to specific symptoms of the disease, requiring mechanistic measurements. There were small sample sizes and many comparisons, inflating the chances of false discovery.

Conclusions

These data are important because they lend support for PwMS becoming engaged not only in exercise in general but in high-intensity exercise in particular.[54] Exercise intensity and frequency are implicated in retaining motor skills through neuroplasticity, underlying the consolidation of motor skills into motor memory.[9] An important result was that 25 sessions of exercise of any type did not exacerbate MS symptoms.[54-57]

Recent reviews of exercise studies in patients with neurodegenerative diseases, including MS, identified no studies that were longer than 12 months, and none included a maintenance program after an initial exercise period.[6,7,9] Long-term exercise intervention studies are needed because the favorable effects tend to disappear after the exercise stimulus is withdrawn, implying the need to incorporate exercise and physical activity daily into the lives of PwMS.[6,7,9,17,50] Our approach differed from previous long-term exercise studies in PwMS that used 1-3 sessions per week for up to 12 months.[7,10-13,58] Instead, we wished to extend the current shift in paradigm to using a high-intensity and high-frequency exercise conditioning period of 5 weeks (25 sessions).[8,9,53-57,59,60] We sought to determine if the initial exercise effects can be boosted or at least sustained by a thrice weekly maintenance

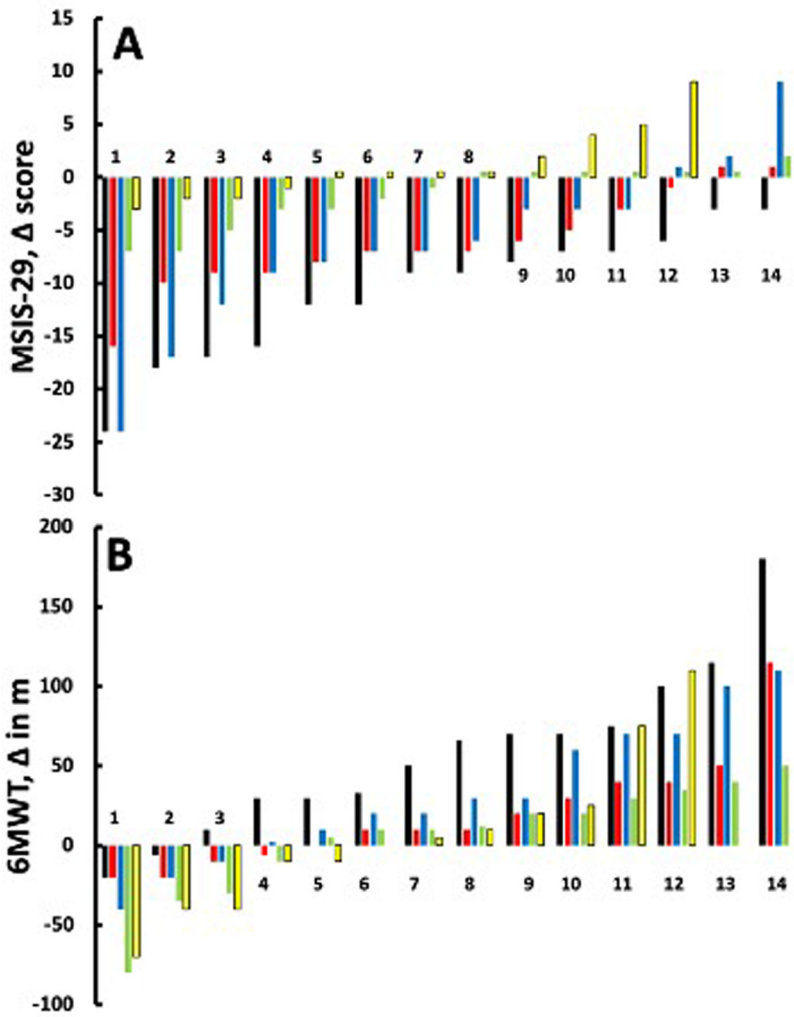

Fig 3 Change scores (Δ) in individual patients in MSIS-29 (primary outcome [A]) and 6MWT (B). Black, exergaming training; Blue, cycling training; Green, proprioceptive neuromuscular facilitation training; Red, balance training; Yellow, control group (n=12, all other groups n=14).

program for 2 years, a design, to our knowledge, not yet used (see fig 1, supplement 1, available online only at http://www.archives-pmr.org/). We found that any of 4 forms of exercise maintenance slowed symptom worsening and improved QOL with EXE producing the greatest effects. The maintenance program further increased (ie, potentiated) the initial exercise effects so that at 24 months there were substantial and clinically meaningful differences in scores favoring EXE vs the control group in MSIS-29 (40 points), EQ-5D index (7 points), TAT (8 points), BBS (12 points), and 6MWT (135m). These data add to and complement the scant and mostly inconsistent long-term exercise data in MS.[7,10-13,58]

In conclusion, 25 sessions of EXE, BAL, CYC, and PNF, in this order, improved clinical and motor symptoms and QOL and subsequent, 2-year-long thrice weekly maintenance programs further slowed symptom worsening and improved QOL. EXE was the most effective and PNF was the least effective to improve clinical symptoms, motor function, and QOL in PwMS.

Suppliers

a. Posture Evaluation Platform; MED-EVAL KFT, MediTECH Electronic GmbH, 95.

b. Microsoft Xbox 360 Core System with Kinect; Microsoft Corp.

c. Statistical Package for the Social Sciences, SPSS, version 22; IBM.

Keywords

Posture; Rehabilitation

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References

1. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med 2018;378:169–80.
2. Centonze D, Leocani L, Feys P. Advances in physical rehabilitation of multiple sclerosis. Curr Opin Neurol 2020;33:255–61.

3. Lozinski BM, Yong VW. Exercise and the brain in multiple sclerosis. Mult Scler 2022;28:1167–72.
4. Prosperini L, Di Filippo M. Beyond clinical changes: rehabilitation-induced neuroplasticity in MS. Mult Scler 2019;25:1348–62.
5. Silva BA, Miglietta EA, Ferrari CC. Training the brain: could it improve multiple sclerosis treatment? Rev Neurosci 2020;31:779–92.
6. Dalmazane M, Gallou-Guyot M, Compagnat M, et al. Effects on gait and balance of home-based active video game interventions in persons with multiple sclerosis: a systematic review. Mult Scler Relat Disord 2021;51:102928.
7. Devasahayam AJ, Downer MB, Ploughman M. The effects of aerobic exercise on the recovery of walking ability and neuroplasticity in people with multiple sclerosis: a systematic review of animal and clinical studies. Mult Scler Int 2017;2017:4815958.
8. Kim Y, Mehta T, Lai B, Motl RW. Immediate and sustained effects of interventions for changing physical activity in people with multiple sclerosis: meta-analysis of randomized controlled trials. Arch Phys Med Rehabil 2020;101:1414–36.
9. Prosperini L, Tomassini V, Castelli L, et al. Exergames for balance dysfunction in neurological disability: a meta-analysis with meta-regression. J Neurol 2021;268:3223–37.
10. Hansen D, Wens I, Keytsman C, Eijnde BO, Dendale P. Is long-term exercise intervention effective to improve cardiac autonomic control during exercise in subjects with multiple sclerosis? A randomized controlled trial. Eur J Phys Rehabil Med 2015;51:223–31.
11. Schmidt S, Wonneberger M. Long-term endurance exercise improves aerobic capacity in patients with relapsing-remitting multiple sclerosis: impact of baseline fatigue. J Neurol Sci 2014;336:29–35.
12. Romberg A, Virtanen A, Ruutiainen J. Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. J Neurol 2005;252:839–45.
13. Collett J, Dawes H, Meaney A, et al. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. Mult Scler 2011;17:594–603.
14. Dennett R, Madsen LT, Connolly L, Hosking J, Dalgas U, Freeman J. Adherence and drop-out in randomized controlled trials of exercise interventions in people with multiple sclerosis: A systematic review and meta-analyses. Mult Scler Relat Disord 2020;43:102169.
15. Reynolds ER, Ashbaugh AD, Hockenberry BJ, McGrew CA. Multiple sclerosis and exercise: a literature review. Curr Sports Med Rep 2018;17:31–5.
16. Parra-Moreno M, Rodriguez-Juan JJ, Ruiz-Cardenas JD. Use of commercial video games to improve postural balance in patients with multiple sclerosis: a systematic review and meta-analysis of randomised controlled clinical trials. Neurologia (Engl Ed) 2018 Mar 7. [Epub ahead of print].
17. Motl RW, Sandroff BM, Kwakkel G, et al. Exercise in patients with multiple sclerosis. Lancet Neurol 2017;16:848–56.
18. Baird JF, Motl RW. Response heterogeneity with exercise training and physical activity interventions among persons with multiple sclerosis. Neurorehabil Neural Repair 2019;33:3–14.
19. Kerling A, Keweloh K, Tegtbur U, et al. Effects of a short physical exercise intervention on patients with multiple sclerosis (MS). Int J Mol Sci 2015;16:15761–75.
20. Kramer A, Dettmers C, Gruber M. Exergaming with additional postural demands improves balance and gait in patients with multiple sclerosis as much as conventional balance training and leads to high adherence to home-based balance training. Arch Phys Med Rehabil 2014;95:1803–9.
21. Cakt BD, Nacir B, Genc H, et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. Am J Phys Med Rehabil 2010;89:446–57.
22. Rasova K, Havrdova E, Brandejsky P, Zalisova M, Foubikova B, Martinkova P. Comparison of the influence of different rehabilitation programmes on clinical, spirometric and spiroergometric parameters in patients with multiple sclerosis. Mult Scler 2006;12:227–34.
23. Razazian N, Yavari Z, Farnia V, et al. Exercising impacts on fatigue, depression, and paresthesia in female patients with multiple sclerosis. Med Sci Sports Exerc 2016;48:796–803.
24. Sadeghi Bahmani D, Razazian N, Farnia V, Alikhani M, Tatari F, Brand S. Compared to an active control condition, in persons with multiple sclerosis two different types of exercise training improved sleep and depression, but not fatigue, paresthesia, and intolerance of uncertainty. Mult Scler Relat Disord 2019;36:101356.
25. Korkmaz NC, Kirdi N, Temucin CM, Armutlu K, Yakut Y, Karabudak R. Improvement of muscle strength and fatigue with high voltage pulsed galvanic stimulation in multiple sclerosis patients—a non-randomized controlled trial. J Pak Med Assoc 2011;61:736–43.
26. Yazgan YZ, Tarakci E, Tarakci D, Ozdincler AR, Kurtuncu M. Comparison of the effects of two different exergaming systems on balance, functionality, fatigue, and quality of life in people with multiple sclerosis: a randomized controlled trial. Mult Scler Relat Disord 2019;39:101902.
27. Tollár J, Nagy F, Tóth BE, et al. Exercise effects on multiple sclerosis quality of life and clinical-motor symptoms. Med Sci Sports Exerc 2020;52:1007–14.
28. Tollár J, Nagy F, Hortobágyi T. Vastly different exercise programs similarly improve parkinsonian symptoms: a randomized clinical trial. Gerontology 2019;65:120–7.
29. Tollár J, Nagy F, Kovács N, Hortobágyi T. A high-intensity multicomponent agility intervention improves Parkinson patients' clinical and motor symptoms. Arch Phys Med Rehabil 2018;99:2478–84.
30. Tollár J, Nagy F, Kovács N, Hortobágyi T. Two-year agility maintenance training slows the progression of parkinsonian symptoms. Med Sci Sports Exerc 2019;51:237–45.
31. Tollár J, Nagy F, Moizs M, Tóth BE, Sanders LMJ, Hortobágyi T. Diverse exercises similarly reduce older adults' mobility limitations. Med Sci Sports Exerc 2019;51:1809–16.
32. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain 2001;124:962–73.
33. Riazi A, Hobart JC, Lamping DL, Fitzpatrick R, Thompson AJ. Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital based samples. J Neurol Neurosurg Psychiatry 2002;73:701–4.
34. Kuspinar A, Mayo NE. A review of the psychometric properties of generic utility measures in multiple sclerosis. Pharmacoeconomics 2014;32:759–73.
35. Subica AM, Fowler JC, Elhai JD, et al. Factor structure and diagnostic validity of the Beck Depression Inventory-II with adult clinical inpatients: comparison to a gold-standard diagnostic interview. Psychol Assess 2014;26:1106–15.
36. Kegelmeyer DA, Kloos AD, Thomas KM, Kostyk SK. Reliability and validity of the Tinetti Mobility Test for individuals with Parkinson disease. Phys Ther 2007;87:1369–78.
37. Cattaneo D, Regola A, Meotti M. Validity of six balance disorders scales in persons with multiple sclerosis. Disabil Rehabil 2006;28:789–95.
38. Decavel P, Moulin T, Sagawa Jr. Y. Gait tests in multiple sclerosis: reliability and cut-off values. Gait Posture 2019;67:37–42.
39. Wajda DA, Motl RW, Sosnoff JJ. Three-month test-retest reliability of center of pressure motion during standing balance in individuals with multiple sclerosis. Int J MS Care 2016;18:59–62.
40. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.
41. Costelloe L, O'Rourke K, Kearney H, et al. The patient knows best: significant change in the physical component of the Multiple Sclerosis Impact Scale (MSIS-29 physical). J Neurol Neurosurg Psychiatry 2007;78:841–4.
42. Cohen J. Statistical power for the behavioral sciences. Hillsdale, NJ: Erblaum; 1988.
43. Garrett M, Hogan N, Larkin A, Saunders J, Jakeman P, Coote S. Exercise in the community for people with minimal gait impairment due to

MS: an assessor-blind randomized controlled trial. Mult Scler 2013;19:782–9.
44. Prosperini L, Fortuna D, Gianni C, Leonardi L, Marchetti MR, Pozzilli C. Home-based balance training using the Wii balance board: a randomized, crossover pilot study in multiple sclerosis. Neurorehabil Neural Repair 2013;27:516–25.
45. Di Tella S, Pagliari C, Blasi V, Mendozzi L, Rovaris M, Baglio F. Integrated telerehabilitation approach in multiple sclerosis: a systematic review and meta-analysis. J Telemed Telecare 2020;26:385–99.
46. Wiles CM, Newcombe RG, Fuller KJ, et al. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. J Neurol Neurosurg Psychiatry 2001;70:174–9.
47. Edwards T, Pilutti LA. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: a systematic review and future research directions. Mult Scler Relat Disord 2017;16:31–9.
48. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch Phys Med Rehabil 2013;94:1800–28.
49. Brichetto G, Spallarossa P, de Carvalho ML, Battaglia MA. The effect of Nintendo(R) Wii(R) on balance in people with multiple sclerosis: a pilot randomized control study. Mult Scler 2013;19:1219–21.
50. Straudi S, Fanciullacci C, Martinuzzi C, et al. The effects of robot-assisted gait training in progressive multiple sclerosis: a randomized controlled trial. Mult Scler 2016;22:373–84.
51. Timmermans ST, de Groot V, Beckerman H. Ten-year disease progression in multiple sclerosis: walking declines more rapidly than arm and hand function. Mult Scler Relat Disord 2020;45:102343.
52. Hvid LG, Feys P, Baert I, Kalron A, Dalgas U. Accelerated trajectories of walking capacity across the adult life span in persons with multiple sclerosis: an underrecognized challenge. Neurorehabil Neural Repair 2020;34:360–9.
53. Zaenker P, Favret F, Lonsdorfer E, Muff G, de Seze J, Isner-Horobeti ME. High-intensity interval training combined with resistance training improves physiological capacities, strength and quality of life in multiple sclerosis patients: a pilot study. Eur J Phys Rehabil Med 2018;54:58–67.
54. Wens I, Dalgas U, Vandenabeele F, et al. High intensity aerobic and resistance exercise can improve glucose tolerance in persons with multiple sclerosis: a randomized controlled trial. Am J Phys Med Rehabil 2017;96:161–6.
55. Orban A, Garg B, Sammi MK, et al. Effect of high-intensity exercise on multiple sclerosis function and phosphorous magnetic resonance spectroscopy outcomes. Med Sci Sports Exerc 2019; 51:1380–6.
56. Manca A, Martinez G, Cereatti A, et al. Isokinetic predictors of gait speed increase following high-intensity resistance training of the ankle dorsiflexors in people with multiple sclerosis: a pilot study. Clin Biomech (Bristol, Avon) 2019;67:102–6.
57. Keytsman C, Hansen D, Wens I, O Eijnde B. Impact of high-intensity concurrent training on cardiovascular risk factors in persons with multiple sclerosis - pilot study. Disabil Rehabil 2019;41: 430–5.
58. Thomas S, Fazakarley L, Thomas PW, et al. Mii-vitaliSe: a pilot randomised controlled trial of a home gaming system (Nintendo Wii) to increase activity levels, vitality and well-being in people with multiple sclerosis. BMJ Open 2017;7:e016966.
59. Steen Krawcyk R, Vinther A, Petersen NC, et al. Effect of home-based high-intensity interval training in patients with lacunar stroke: a randomized controlled trial. Front Neurol 2019;10:664.
60. Kolmos M, Krawcyk RS, Kruuse C. Effect of high-intensity training on endothelial function in patients with cardiovascular and cerebrovascular disease: a systematic review. SAGE Open Med 2016; 4:2050312116682253.