Supplementary Online Content

Shulman LM, Katzel LI, Ivey FM, et al. Randomized clinical trial of 3 types of physical exercise for patients with Parkinson disease. *Arch Neurol*. Published online November 5, 2012. doi:10.1001/jamaneurol.2013.646.

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eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

eMethods

1. Protocol for Screening Treadmill Exercise Test

All eligible subjects received a screening treadmill exercise test to determine cardiopulmonary safety and neuromotor capacity to participate. The subjects started at zero incline and at their self-selected walking speed as determined by timed floor walks. In some subjects the speed of the treadmill was adjusted slightly upwards or downwards based on feedback from the subjects and observations of the research team conducting the test. Overall the initial speed on the treadmill was 94% of their self-selected floor walking speed. The incline was gradually increased at the pre-selected constant velocity to assess cardiopulmonary response and safety of more strenuous exercise. Handrail support was minimized, a gait safety belt was worn at all times, and tests were physician-supervised with continuous vital signs and ECG monitoring. Subjects needed to achieve three minutes TM walking at >0.3 MPH for study entry.

2. Protocol for Assessment of VO_2 Peak

Protocol for assessment of VO_2 peak was conducted as previously described [1] using a Quark Cardio Pulmonary Exercise Testing metabolic analyzer (Cosmed, Rome, Italy). The treadmill tests were started at the self-selected walking speed determined on the screening exercise treadmill test and 0% grade. The grade was increased to 4% at 2 minutes, and then increased by 2% every minute from minute 4 until the subjects reached voluntary exhaustion. In a few subjects based on the observations of the research team, the speed was readjusted during the treadmill test. During the graded treadmill walking, O_2 consumption, CO_2 production, and minute ventilation were measured breath-by-breath and values averaged for 20 second intervals. The physician supervising the test (LIK) was blinded to the results of the screening test and prior measurements of VO_2. Based on our pilot study [2], we anticipated that deconditioned subjects would not be able to obtain maximal aerobic capacity, defined as a plateau in oxygen consumption during the final stage, maximal heart rate > 85% of age-adjusted predicted maximal heart rate, and respiratory quotient (RQ)> 1.10. The VO_2 peak was therefore determined based on the average of the final two 20 second averages obtained during the final stage of the test. Since reliability of fitness testing was not previously established in PD, all subjects performed 2 fitness tests (1 week apart) both before and after training to avoid fatigue. The highest of the 2 values was accepted as the $V0_2$ max or peak. The intra-class correlation coefficients for VO_2 peak (in ml/kg/min or L/min) were highly reliable with ICC of 0.90 and 0.96 respectively [1].

3. Implementation of Exercise Training Subgroups Protocols

The training for the 3 exercise subgroups were implemented as per protocol. HIT subjects increased their treadmill speed over three months by an average of 60% ($p<0.001$ within group) compared to a 5% increase in LIT (NS within group; $p<0.001$ between groups). All LIT subjects increased training duration from 15 to 50 minutes per session (mean change 233%) compared to an increase from 15 to 30 minutes in all HIT subjects (mean change 100%). S-R subjects significantly increased their resistance on all three training machines with a 47% increase on Leg Press, 50% increase on Knee Extension and 55% increase on Leg Curl (all $p<0.001$). LIT subjects were at their target duration for four weeks and their target heart rate for all 12 weeks. HIT subjects were at their target duration for eight weeks and their target heart rate for 10 weeks.

4. Addendum to Methods and Statistical Analysis

Sample size was determined based on our pilot study [2]. The eTable 1 shows the sample size needed to detect differences between treatment and controls on a range of outcomes with 80-90% power. We planned to enroll 66 subjects (22 per group) to complete a minimum of 19 in the HIT, LIT and S-R groups (N=57 total), accounting for 15% attrition. This sample size detects differences with 80-90% power (alpha=0.05, two-tailed), in the primary outcome measure (6-minute walk).
In the study, we actually enrolled 80 subjects, and completed a total of 67 subjects (22-23 per group).

A random number generator allocated (block randomized) eligible subjects into one of three exercise groups in a 1:1:1 ratio: 1) HIT, 2) LIT or 3) S-R. The study biostatistician (JDS) generated the random allocation sequence and the sequence was implemented by the study coordinator without exception. The study coordinator notified study subjects of their exercise group when they arrived for their first day of exercise

training, following both the screening treadmill exercise test and the assessment of VO2 peak. Baseline and post-training assessments were performed by physicians and staff blinded to subjects' treatment group.

References for eDocuments

1. Katzel LI, Sorkin JD, Macko RF, Smith B, Ivey FM, Shulman LM. Repeatability of Aerobic Capacity Measurements in Parkinson Disease. Med Sci Sports Exerc 2011.
2. Skidmore F, Patterson S, Shulman LM, Sorkin J, Macko R. Pilot Safety and Feasibility Study of Aerobic Treadmill Exercise in Parkinson's Disease with Gait Impairment. Journal of Rehabilitation Research & Development 2008;45:117-24.

eTable 1. Sample Analysis	**Sample Size Per Group arm**	
Outcome Measure	**Power=.8 Alpha=.05**	**Power =.9 Alpha = .05**
***6-Minute Walk**	**15**	**19**
Home Ambulatory Activity	16	22
Ambulatory Workload (Mets)	6	8
UPDRS Total Score	5	6
UPDRS Motor Score	9	12
*Indicates key outcome for powering study.		

eTable 2. Disease Severity, Disability and Non-motor Outcomes Following Exercise in Parkinson's Disease (N=67)

			Pre-Training		Post-Training		Change				
Measure	Arm	N	Mean	SE	Mean	SE	Mean	SE	[%] *	SE	Within Group Comparison p value*
Disease Severity, Disability, & Activity											
	HIT	23	45.2	2.5	43.9	2.8	-1.35	1.7	[-1.5]	4.1	0.481
Total	LIT	22	46.6	2.7	48.2	3.0	1.64	2.3	[5.8]	6.1	0.404
UPDRS	S-R	22	48.2	3.3	45.3	3.5	-2.95	1.8	[-4.8]	4.1	0.134
	HIT	23	30.3	2.0	30.0	2.2	-0.26	1.5	[1.6]	5.5	0.874
Motor	LIT	22	31.6	2.0	33.7	2.2	2.09	2.1	[12.1]	9.1	0.217
UPDRS	S-R	22	34.5	2.3	31.0	2.3	-3.45	1.3	[-9.0]	3.9	0.043[a]
Schwab	HIT	23	82.6	1.1	82.6	1.1	0	1.3	[0.3]	1.5	1.000
and	LIT	22	80.0	2.3	81.4	2.2	1.36	2.1	[2.8]	3.4	0.421
England	S-R	22	81.4	2.1	83.2	2.5	1.82	1.6	[2.4]	2.1	0.284
SAM	HIT	22	7618.2	548.5	7558.6	728.9	-59.59	650.7	[6.1]	10.7	0.927
(# steps	LIT	21	8440.2	785.5	8646.5	881.1	206.3	798.7	[13.2]	15.8	0.756
per day)	S-R	22	7844.3	751.4	7429.0	612.8	-415.3	478.9	[3.0]	10.0	0.523
	HIT	23	12.1	0.7	11.7	0.8	-0.42	0.4	[-3.5]	2.7	0.360
TUG	LIT	21	10.7	0.7	10.2	0.7	-0.52	0.2	[-4.7]	1.9	0.268
	S-R	22	11.7	1.0	12.2	1.5	0.56	0.7	[2.0]	4.0	0.235
Non-Motor Assessments											
Beck	HIT	23	8.7	1.1	10.1	1.4	1.43	1.0	[36.9]	19.6	0.085
Depression	LIT	22	10.1	1.2	9.4	1.3	-0.68	0.6	[-5.2]	8.0	0.419
Inventory	S-R	22	7.5	0.8	8.2	1	0.68	0.8	[23.5]	15.0	0.419
	HIT	23	48.7	3.5	49.2	3.3	0.52	2.1	[4.8]	7.0	0.809
PD Fatigue	LIT	22	44.1	2.5	45.9	3.2	1.73	2.3	[4.8]	5.1	0.434
Scale	S-R	22	41.3	3.3	41.8	3.3	0.55	2.2	[4.3]	4.4	0.805
PDQ-39	HIT	23	19.8	2.3	20.3	2.6	0.46	2.3	[14.5]	13.3	0.790
Summary	LIT	22	19.7	2.3	19.5	2.6	-0.22	1.3	[-1.0]	5.6	0.898
Index	S-R	21	17.8	2.5	20.5	3	2.70	1.3	[21.3]	12.1	0.125
Falls	HIT	23	20.61	2.5	19.35	2.1	-1.26	1.8	[6.5]	9.5	0.472
Efficacy	LIT	22	19.18	1.8	20.95	3.1	1.77	1.7	[6.3]	7.1	0.324
Scale	S-R	22	24.73	3.8	26.05	4.3	1.32	1.8	[5.2]	6.9	0.463

[a] <0.05

[*] [%] = mean of the within-person percentage changes