Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting

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ABSTRACT

Objectives: To (1) investigate effects of aerobic walking on motor function, cognition, and quality of life in Parkinson disease (PD), and (2) compare safety, tolerability, and fitness benefits of different forms of exercise intervention: continuous/moderate intensity vs interval/alternating between low and vigorous intensity, and individual/neighborhood vs group/facility setting.

Methods: Initial design was a 6-month, 2×2 randomized trial of different exercise regimens in independently ambulatory patients with PD. All arms were required to exercise 3 times per week, 45 minutes per session.

Results: Randomization to group/facility setting was not feasible because of logistical factors. Over the first 2 years, we randomized 43 participants to continuous or interval training. Because preliminary analyses suggested higher musculoskeletal adverse events in the interval group and lack of difference between training methods in improving fitness, the next 17 participants were allocated only to continuous training. Eighty-one percent of 60 participants completed the study with a mean attendance of 83.3% (95% confidence interval: 77.5%–89.0%), exercising at 46.8% (44.0%–49.7%) of their heart rate reserve. There were no serious adverse events. Across all completers, we observed improvements in maximum oxygen consumption, gait speed, Unified Parkinson's Disease Rating Scale sections I and III scores (particularly axial functions and rigidity), fatigue, depression, quality of life (e.g., psychological outlook), and flanker task scores ($p < 0.05$ to $p < 0.001$). Increase in maximum oxygen consumption correlated with improvements on the flanker task and quality of life ($p < 0.05$).

Conclusions: Our preliminary study suggests that aerobic walking in a community setting is safe, well tolerated, and improves aerobic fitness, motor function, fatigue, mood, executive control, and quality of life in mild to moderate PD.

Classification of evidence: This study provides Class IV evidence that in patients with PD, an aerobic exercise program improves aerobic fitness, motor function, fatigue, mood, and cognition. *Neurology*® 2014;83:413–425

GLOSSARY

CFT = Complex Figure Test; **FSS** = Fatigue Severity Scale; **HR$_{max}$** = maximal heart rate; **HRR** = heart rate reserve; **PD** = Parkinson disease; **PDQUALIF** = Parkinson's Disease Quality of Life Scale; **PIS** = percent increase score; **RT** = reaction time; **UPDRS** = Unified Parkinson's Disease Rating Scale; **V̇o$_2$** = maximum oxygen uptake.

Aerobic exercise may be a useful supplemental treatment in Parkinson disease (PD)[1,2] because it improves fitness, executive functions,[3,4] fatigue,[5] depression,[6] and quality of life[7] in aging and chronic disease, and provides neuroprotective effects in animal models of PD.[8,9] Although patients with PD attain fitness benefits from aerobic exercise,[10–13] information on its potential benefits on cognition and quality of life is limited.[1,14–16] Generalizability of findings from fully[11,12] or partially[10] laboratory-based aerobic exercise interventions that used special equipment (e.g., treadmill[10] with safety harness[11,13] or tandem exercise bicycle[12]) to community setting where walking is the most common aerobic exercise[17] is unclear.[2]

Supplemental data at Neurology.org

Motivated by reported improvements in aerobic fitness and ability to inhibit conflicting information (a key executive function) on Eriksen flanker task after a 6-month aerobic walking intervention in normal sedentary elderly,[3] we conducted a phase I/II study to investigate effects of aerobic exercise on motor function, cognition, and quality of life in patients with mild to moderate PD. To identify the best method to deliver fitness training, we also aimed to compare safety, tolerability, and fitness benefits between different training methods (continuous/moderate intensity vs interval/alternating between low and vigorous intensity) and exercise settings (individual vs group). Interval training reportedly facilitates higher fitness gains than continuous training.[18] Group training may promote success through social interaction,[3] whereas individual training offers greater flexibility.

METHODS More details of methods can be found in appendix e-1 on the *Neurology*® Web site at Neurology.org.

Participants. The participants were recruited in Spring 2009, 2010, and 2011 through regional newspaper advertisements and solicitations in the Movement Disorders Clinic at the University of Iowa and the Veterans Affairs Medical Center of Iowa City. We phone screened respondents and evaluated eligible candidates in-person using clinical examination, Mini-Mental State Examination, 12-lead ECG, blood count and biochemistry, followed by graded exercise test using cycle ergometry within 1 week of starting the intervention. At each visit, we obtained body weight and height, heart rate, and blood pressure after 5 minutes of supine rest[19] and after 3 minutes of standing. Throughout the study, the medications of participants continued to be managed by their treating neurologists.

Inclusion criteria. Inclusion criteria were as follows: idiopathic PD, Hoehn and Yahr stage 1–3, men or women aged 50–80 years, and stable dopaminergic treatment regimen for at least 4 weeks before baseline not requiring adjustment.

Exclusion criteria. Exclusion criteria included the following: current participation in an aerobic exercise program; Mini-Mental State Examination score <24; confounding medical, orthopedic, or psychiatric disorders; and cardiac abnormalities during cycle ergometry.

Historical controls. We compared the baseline cognitive performance of our PD cohort with control participants of similar age from our driving studies.[20]

Standard protocol approvals, registrations, and patient consents. The study was approved by the Institutional Review Boards and Human Subjects Office of the University of Iowa and registered at clinicaltrials.gov as NCT00784563, "Effects of Aerobic Exercise in Parkinson's Disease." All participants provided written informed consent.

Design. Initial design was a 2 × 2 randomized trial of different training methods (continuous vs interval) and settings (individual vs group). Sample size was estimated using 80% power to detect an effect size of 0.66 SD in maximum oxygen uptake ($\dot{V}O_2$max) (estimated improvement = 10%/estimated SD of change = 15%) within each arm at $\alpha = 0.05$ and an attrition rate of 25%.

During the first 2 years, the participants were randomized in blocks of 4 to continuous or interval training. Logistical factors (e.g., rural residence) precluded randomization to group setting, leading to convenience-based assignments in the first year, and dropping of the group setting afterward. In the third year, all participants were assigned to the continuous arm after preliminary analyses of prior data raised safety concerns about interval training.

Intervention. The maximal heart rate (HR_{max}) in the exercise prescription was based on age[19] and reduced by 20% in participants who used β-blockers.[21] The duration of exercise sessions (3×/wk) was advanced from 15 to 45 minutes over the first 6 weeks. The goal for continuous training was to remain within 70% to 80% of HR_{max} throughout the session (figure e-1A). Interval trainees alternated every 3 minutes between slower (60%–70% of HR_{max}) and faster (80%–90% of HR_{max}) walking (figure e-1B).[18] We emphasized that these parameters were for guidance only and that the participants should give their best effort without feeling uncomfortable or unsafe.

Participants were asked to wear electronic heart rate and walking speed monitors (Polar RS400, Kempele, Finland) and fill out diaries for each session. A trainer facilitated group training at a track and collected monitor data and exercise diaries. Trainers conducted home visits for the individual arm participants to choose walking routes (a primary outdoor route and an alternative indoor route) and orient the participant about safe exercise procedures, followed by biweekly home visits to monitor safety and compliance.

Efficacy measures. The participants were tested while on their usual antiparkinsonian regimen, always with adequate symptom control to allow comfortable participation in the protocol, at baseline and at the end of the intervention by evaluators blinded to the treatment arm, but not to pre-post training status.

Aerobic fitness. Oxygen uptake was measured from expired air samples on a breath-by-breath basis during cycle ergometry. We verified maximal effort when 2 of 3 criteria were met[22]: (1) a plateau in oxygen uptake between 2 or more workloads, (2) respiratory exchange ratio ≥1.10, and (3) heart rate ≥85% of the age-predicted HR_{max}.

Cognition. Because of sensitivity of the Eriksen flanker task performance to changes in aerobic fitness status,[3,23] we chose change in percent increase score (PIS) on flanker task as the primary cognitive outcome measure. Participants were asked to identify the orientation of a central arrow cue ("<" or ">"), which was flanked on both sides by 2 arrow cues that either pointed in the same direction (congruent: <<<<<) or a different direction (incongruent: >><>>). Using reaction times (RTs) during congruent and incongruent trials, the PIS was calculated as follows: ([RT_incongruent − RT_congruent]/RT_congruent) × 100.[3] The Stroop test was used as another measure of inhibition.

We assessed set shifting using Wisconsin Card Sorting Test and Trail Making Test (B-A),[20] visual perception using Judgment of Line Orientation and Complex Figure Test–Copy, verbal memory using Rey Auditory Verbal Learning Test, visual memory using Complex Figure Test–Recall, language using Controlled Oral Word Association Test,[20] and general cognition using Montreal Cognitive Assessment.[24]

Parkinsonism. Parkinsonism was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) and timed motor tests

(7-m Walk and finger tapping),[25] Functional Reach test for balance,[20] total daily levodopa equivalents,[26] and a patient diary.[27]

Quality of life. The following scales were used to assess quality of life: Fatigue Severity Scale (FSS),[28] Geriatric Depression Scale,[20] and PD Quality of Life Scale (PDQUALIF).[29]

Statistical analysis. Two-sample *t* tests, Wilcoxon rank-sum, or Fisher exact tests were used to compare baseline features and exercise characteristics and outcomes between different treatment arms, and between the completers and dropouts, and to compare baseline cognitive performance of our PD participants with controls from our driving studies.[20] Regression methods were used to adjust these comparisons for age, education, and sex.

Because all treatment arms were designed to deliver a similar average aerobic intensity, we planned to pool a priori all completers throughout the study to analyze the effects of aerobic exercise with higher statistical power. We used Wilcoxon signed-rank tests or paired *t* tests to compare final vs baseline outcomes. When a significant change in outcomes was observed, we used regression models to assess and adjust for the effect of different settings and training methods, calendar year, and change in levodopa equivalent. We also used Pearson correlations and regression models to quantify associations of changes in outcomes with changes in aerobic fitness.

Classification of evidence. The primary research question was whether aerobic exercise could improve aerobic fitness, motor function, quality of life, and cognition in patients with mild to moderate PD. This interventional study presents Class IV level of evidence that aerobic walking improves aerobic fitness, motor function, fatigue, mood, and cognition.

For the other research question on the method of delivery of fitness training, this study provides Class II evidence that varying-intensity interval exercise compared with continuous, moderate exercise does not improve aerobic fitness and gait speed in patients with PD.

RESULTS Participants. Of the 104 candidates with PD screened in person (90 community responders to newspaper advertisements and 14 clinic patients), 60 participants started the intervention (table 1). Thirty-six candidates did not meet eligibility criteria and 8 declined participation because of time commitment. Compared with healthy elderly from our past driving studies,[20] our PD cohort had mild cognitive deficits in various domains (table e-1). We did not have flanker task results in controls, but the level of interference in our patients with PD appeared to be above that observed in healthy elderly,[3] consistent with prior reports in PD.[30]

Tolerability and safety. *The randomized segment.* Over the first 2 years, we screened 76 and randomized 43 participants to continuous (n = 21) or interval (n = 22) training arms (figure 1), who did not have demographic, motor, or cognitive differences at baseline except for better depression and quality of life scores in the interval group (table 2). Nine participants (continuous = 4, interval = 5) from an urban region were assigned to group setting.

Thirty-five participants completed the program, indicating a 19% attrition rate (table 2). Three participants in the interval group dropped out because of exercise-related adverse events (knee pain, reversible with rest and conservative measures) whereas no participant in the continuous group dropped out because of exercise-related adverse events. The following reasons for dropping out were deemed not related to exercise: farming accident (n = 1), urinary tract infection (n = 1), depression associated with social circumstances (n = 1), starting a weight-gain program for preexisting weight loss (n = 1), and worsening of neuropathic pain with analgesic adjustment (n = 1).

Heart rate variability was significantly higher in the interval group as expected, but there were no significant differences in attendance, adherence to heart rate goal, or changes in $\dot{V}O_2max$ or gait speed on 7-m Walk Test (table 2). Because of potentially increased risk without additional fitness benefits, we eliminated the interval group for the third year.

The third year. We screened 28 participants and assigned all 17 eligible participants to the continuous/individual arm. Fourteen participants completed the intervention. A participant dropped out because of exercise-related hip pain. Although a participant with preexisting venous circulation problems denied association of increased leg pain during the study with exercise, we recommended discontinuation. The third dropout was due to developing common peroneal neuropathy after prolonged squatting for laying tiles.

Overall. There were no significant demographic, fitness, motor, or cognitive differences at baseline between completers (n = 49) and dropouts (n = 11) except for better fatigue scores and tendencies for higher use of β-blockers, and better quality of life and depression scores in the dropouts (table 1). The dropouts exercised at significantly higher percentage of heart rate at anaerobic threshold and showed higher heart rate variability (table 1).

There were no serious adverse events throughout the study. Four participants dropped out because of probably/definitely exercise-related musculoskeletal adverse events. Self-limited, exercise-related adverse events of mild to moderate severity included muscle strain (n = 5 participants), shortness of breath (n = 12), dizziness (n = 4), neck pain (n = 2), low back pain (n = 1), and falls with no or minor injury (n = 3).

Attendance and adherence. The participants completed a total of 3,658 exercise sessions per diaries (96% captured with electronic heart rate monitors) throughout the study. Across the groups and years, the completers attended 83.3% (95% confidence interval: 77.5%–89.0%) of the required sessions over 187 (183–193) days, with the continuous/individual group showing best attendance at 89.7% (82.0%–97.4%). The mean

Table 1 Baseline characteristics of the PD participants (n = 60) and comparison of completers (n = 49) vs dropouts (n = 11)

Domain	All	Completers	Dropouts	p
Demographics				
Age, y	65.4 ± 6.2	65.5 ± 6.4	65.2 ± 5.2	0.905
Sex, % men	68.3	65.3	81.8	0.476
Education, y	15.1 ± 2.3	15.1 ± 2.3	14.9 ± 2.2	0.784
PD history/stage				
Disease duration, y	5.5 ± 4.9	5.2 ± 5.0	6.8 ± 4.4	0.357
HY stage, n, median	HY 1 = 7, HY 2 = 46, HY 2.5 = 6, HY 3 = 1, median = 2	HY 1 = 7, HY 2 = 35, HY 2.5 = 6, HY 3 = 1, median = 2	HY 2 = 11, median = 2	1.000
Disability				
Schwab-England Scale (↑)	90.1 ± 7.0	89.8 ± 7.0	91.4 ± 7.6	0.509
Treatment				
Levodopa preparations, n/(mg/d)	37/(580 ± 298)	28/(581 ± 283)	9/(578 ± 360)	0.982
Pramipexole, n/(mg/d)	14/(3.1 ± 1.5)	13/(3.1 ± 1.5)	1/(3.0)	0.934
Ropinirole, n/(mg/d)	17/(10.4 ± 6.9)	12/(11.7 ± 7.1)	5/(7.5 ± 6.2)	0.270
Selegiline, n/(mg/d)	3/(8.3 ± 2.9)	2/(7.5 ± 3.5)	1/(10)	0.480
Rasagiline, n/(mg/d)	9/(1.0 ± 0.0)	8/(1.0 ± 0.0)	1/(1.0)	1.000
Amantadine, n/(mg/d)	7/(214 ± 69)	5/(200 ± 71)	2/(250 ± 71)	0.388
Trihexyphenidyl, n/(mg/d)	4/(5.5 ± 1.0)	2/(6 ± 0)	1/(6)	0.317
No treatment, n	5	4	1	1.000
Levodopa equivalent, mg/d	589 ± 380	516 ± 369	646 ± 432	0.309
Diary, h/d				
On time	12.9 ± 4.1	12.7 ± 4.5	13.7 ± 2.0	0.470
Off time	2.0 ± 2.5	2.1 ± 2.7	1.7 ± 1.6	0.648
Time with dyskinesia	1.0 ± 2.8	1.1 ± 3.0	0.7 ± 1.5	0.729
Sleep time	8.1 ± 1.3	8.0 ± 1.3	8.3 ± 1.3	0.627
Timed motor tests				
7-m Walk time, s (↓)	9.3 ± 1.5	9.4 ± 1.5	9.1 ± 1.6	0.500
Right finger tapping (↑)	20.2 ± 4.0	20.3 ± 4.0	19.5 ± 4.0	0.549
Left finger tapping (↑)	19.0 ± 3.6	19.1 ± 3.8	18.5 ± 2.8	0.653
Balance				
Functional Reach, in. (↑)	14.8 ± 2.6	14.8 ± 2.9	14.5 ± 1.3	0.717
Aerobic				
$\dot{V}o_2max$, mL/min/kg (↑)	25.2 ± 6.5	24.9 ± 6.7	26.3 ± 5.6	0.550
Vital signs				
Systolic BP-supine, mm Hg	132 ± 13	132 ± 13	133 ± 14	0.854
Diastolic BP-supine, mm Hg	74 ± 7	76 ± 9	73 ± 6	0.313
Pulse-supine, beats/min	65 ± 13	65 ± 13	61 ± 9	0.208
Systolic BP-standing, mm Hg	121 ± 16	121 ± 17	122 ± 15	0.784
Diastolic BP-standing, mm Hg	72 ± 10	72 ± 9	74 ± 12	0.703
Pulse-standing, beats/min	75 ± 12	77 ± 12	70 ± 10	0.069
Body mass index, kg/m^2	27.6 ± 4.6	27.3 ± 4.7	28.7 ± 4.3	0.356
Quality of life				
Fatigue Severity Scale (↓)	3.9 ± 1.1	4.1 ± 1.1	3.1 ± 0.7	0.009[a]
Geriatric Depression Scale (↓)	4.9 ± 3.5	5.3 ± 3.6	3.3 ± 2.8	0.083

Continued

Table 1 Continued

Domain			All	Completers	Dropouts	p
PDQUALIF total score (↓)			40.6 ± 10.5	41.7 ± 8.9	35.8 ± 13.5	0.078
Cognition						
Executive functions	Inhibition	Flanker–PIS (↓)	24.7 ± 9.5	24.9 ± 9.9	23.5 ± 7.8	0.677
		Stroop-Interference (↑)	−4.7 ± 6.4	−4.5 ± 6.3	−5.2 ± 7.0	0.779
	Set shifting	TMT B-A, s (↓)	51.2 ± 32.5	50.3 ± 35.5	54.8 ± 14.0	0.684
		WCST Errors (↓)	36.9 ± 23.4	36.0 ± 25.0	40.7 ± 16.8	0.552
Verbal memory		AVLT-Recall (↑)	8.6 ± 3.6	8.4 ± 3.3	9.4 ± 4.6	0.437
Language		COWA (↑)	37.4 ± 10.7	37.3 ± 10.9	37.8 ± 10.3	0.892
Visuospatial		JLO (↑)	24.1 ± 4.5	23.9 ± 4.7	24.9 ± 3.5	0.496
		CFT-Copy (↑)	28.4 ± 4.1	28.2 ± 4.0	29.5 ± 4.8	0.345
Visual memory		CFT-Recall (↑)	15.8 ± 6.2	15.9 ± 6.2	15.2 ± 6.3	0.717
		BVRT-Error (↓)	5.9 ± 3.6	6.0 ± 3.8	5.5 ± 2.6	0.641
General		MoCA (↑)	24.5 ± 2.9	24.5 ± 3.0	24.5 ± 0.7	0.995
Medication		β-Blocker use, n	10	6	4	0.074
Exercise characteristics						
Training mode		Continuous/interval	38/22	C = 32, I = 17	C = 6, I = 5	0.511
Setting		Individual/group	51/9	I = 42, G = 7	I = 9, G = 2	0.664
Attendance		No. of sessions		67.1 ± 18.0	32.6 ± 18.6	<0.001[a]
Heart rate		HRX, beats/min		108 ± 12	110 ± 11	0.665
		% of HR$_{max}$		69.7 ± 7.1	70.7 ± 5.8	0.681
		% of HRR		46.8 ± 9.8	51.7 ± 8.7	0.132
		% of HRAT		102.0 ± 10.4	114.2 ± 9.6	0.001[a]
HRX variability		SD of HRX		7.1 ± 3.0	10.6 ± 5.1	0.003[a]

Abbreviations: AVLT = Auditory Verbal Learning Test; BP = blood pressure; BVRT = Benton Visual Retention Test; CFT = Complex Figure Test; COWA = Controlled Oral Word Association; HRAT = heart rate at anaerobic threshold; HR$_{max}$ = maximal heart rate; HRR = heart rate reserve; HRX = heart rate during exercise; HY = Hoehn and Yahr; JLO = Judgment of Line Orientation; MoCA = Montreal Cognitive Assessment; PD = Parkinson disease; PDQUALIF = Parkinson's Disease Quality of Life Scale; PIS = percent increase score; TMT B-A = Trail Making Test, subtests B-A; V̇o$_2$max = maximum oxygen uptake; WCST = Wisconsin Card Sorting Test.
Values represent mean ± SD unless indicated otherwise. (↓) = lower better; (↑) = higher better.
[a] Significant values.

exercise heart rate was 107.8 (104.3–111.3) beats per minute, which was standardized as 46.8% (44.0%–49.7%) of heart rate reserve (HRR),[31] and 69.7% (67.7%–71.8%) of age-predicted HR$_{max}$,[31] and 101.9% (99.0%–104.9%) of heart rate at anaerobic (ventilatory) threshold during baseline cycle ergometry,[19] suggesting that participants gave good effort during the exercise. The mean walking speed was 4.6 (4.3–4.9) km/h. There was no significant difference in the observed heart rates (i.e., exercise intensity) and gait speed between the treatment arms.

Efficacy. Because there were no significant differences in baseline characteristics (demographics, fitness, motor function, and cognition) and observed mean exercise intensity and adherence between treatment arms, we proceeded with our a priori analysis plan to pool all completers. We observed significant improvements in various outcome categories (table 3): (1) aerobic fitness and motor function: V̇o$_2$max, 7-m Walk time, and UPDRS subscale III (motor) scores, driven by factors[32] 1 (axial function/gait) and 3 (rigidity); (2) cognition: PIS on the flanker task; and (3) quality of life and other nonmotor functions: scores on various subscales of the PDQUALIF (social role, self-image/sexuality, outlook), FSS, Geriatric Depression Scale, and UPDRS subscale I. The total daily levodopa equivalent stayed the same in 34 of 49 participants, increased in 11, and decreased in 4 (p = 0.057).

Table 4 shows unadjusted and adjusted effect sizes in the significantly improved variables. Adjustment

Figure 1 Flow of participants throughout the study
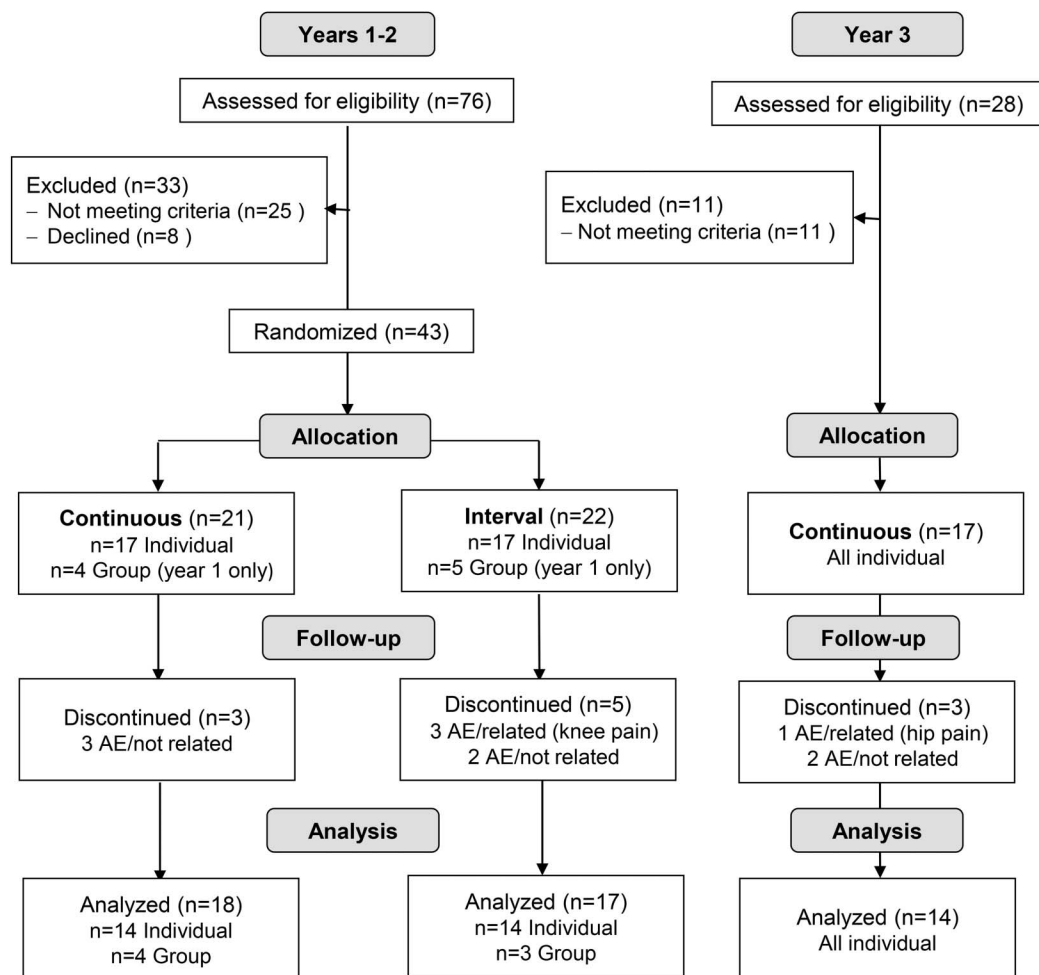
The figure includes the CONSORT (Consolidated Standards of Reporting Trials) diagram for the randomized segment (years 1 and 2). All participants in year 3 were assigned to continuous/individual arm. AE = adverse event.

for changes in total daily levodopa equivalent did not render the observed improvements insignificant. After simultaneous adjustment for different training methods and settings, calendar year, and change in levodopa equivalent (using the standard covariate pattern as the first year of the study, continuous training, individual setting, and no change in levodopa equivalent), the p values for the changes in these variables still remained significant except change in FSS score (adjusted $p = 0.070$). However, the p value for the change in the average PDQUALIF score reached significance (adjusted $p = 0.006$).

Associations of exercise intensity and change in fitness. Increase in $\dot{V}O_2max$ correlated with mean exercise intensity expressed as percentage of HRR ($r = 0.33$, $p = 0.034$), total exercise dose expressed as mean intensity × time walked across all sessions ($r = 0.45$, $p = 0.003$), and mean walking speed ($r = 0.31$, $p = 0.048$). Multiple linear regression models showed that improvements on both the

flanker task and total quality-of-life score were significantly associated with increase in $\dot{V}O_2max$ (for PIS: b = -0.92, $p = 0.040$; for PDQUALIF: b = -0.476, $p = 0.031$) and tended to be associated with lower $\dot{V}O_2max$ at baseline (for PIS: b = 0.339, $p = 0.056$; for PDQUALIF: b = 0.176, $p = 0.070$), but not with change in levodopa equivalent. The changes in gait speed, UPDRS, fatigue, and mood scores were not associated with changes in $\dot{V}O_2max$ or baseline $\dot{V}O_2max$.

DISCUSSION We initiated a 6-month, phase I/II, 2 × 2 randomized trial on aerobic exercise in patients with mild to moderate PD and adapted our design in response to recruitment challenges and safety concerns over the course of the study. We observed improvements in aerobic fitness, motor function, fatigue, mood, and aspects of executive functions and quality of life, which could not be explained by changes in dopaminergic medications

Domain	Continuous	Interval	*p*
Demographics			
Age, y	67.6 ± 7.5	64.7 ± 5.2	0.143
Sex, % men	71.4	68.2	1.000
Education, y	15.9 ± 2.3	14.6 ± 2.3	0.073
PD duration/stage			
Disease duration, y	8.0 ± 6.3	5.3 ± 3.5	0.086
HY stage, n, median	HY 1 = 5, HY 2 = 11, HY 2.5 = 4, HY 3 = 1, median = 2	HY 1 = 5, HY 2 = 19, HY 2.5 = 2, median = 2	0.834
UPDRS			
I: Mental, Mood, Behavior (↓)	2.0 ± 1.8	2.1 ± 2.3	0.824
II: ADL (↓)	10.1 ± 5.1	8.5 ± 5.5	0.328
III: Motor (↓)	19.6 ± 9.9	18.0 ± 10.5	0.833
Disability			
Schwab-England Scale (↑)	88.1 ± 8.9	91.4 ± 5.8	0.159
Treatment			
Levodopa preparations, n/(mg/d)	14/(594 ± 344)	15/(601 ± 273)	0.947
Pramipexole, n/(mg/d)	2/(3.8 ± 3.2)	7/(3.5 ± 1.4)	0.844
Ropinirole, n/(mg/d)	6/(9.0 ± 5.9)	8/(11.9 ± 8.2)	0.436
Selegiline, n/(mg/d)	2/(7.5 ± 3.5)	1/(10)	0.480
Rasagiline, n/(mg/d)	1/(1.0)	2/(1.0 ± 0.0)	1.000
Amantadine, n/(mg/d)	3/(200 ± 0)	2/(200 ± 141)	1.000
Trihexyphenidyl, n/(mg/d)	2/(5.0 ± 1.4)	2/(6.0 ± 0.0)	0.317
No treatment, n	3	0	0.108
Levodopa equivalent, mg/d	531 ± 383	661 ± 387	0.274
Timed motor tests			
7-m Walk time, s (↓)	9.4 ± 1.4	9.5 ± 1.6	0.801
Right finger tapping (↑)	19.6 ± 3.3	20.7 ± 4.1	0.328
Left finger tapping (↑)	18.3 ± 2.7	20.1 ± 3.3	0.066
Balance			
Functional Reach, in. (↑)	14.8 ± 1.9	14.3 ± 3.2	0.506
Aerobic			
V̇o$_2$max, mL/min/kg (↑)	23.4 ± 5.6	25.1 ± 8.2	0.421
Vital signs			
Systolic BP-supine, mm Hg	136 ± 11	133 ± 14	0.464
Diastolic BP-supine, mm Hg	73 ± 7	75 ± 8	0.512
Pulse-supine, beats/min	67 ± 12	64 ± 13	0.433
Systolic BP-standing, mm Hg	125 ± 16	117 ± 16	0.102
Diastolic BP-standing, mm Hg	73 ± 11	70 ± 9	0.291
Pulse-standing, beats/min	77 ± 13	76 ± 10	0.851
Body mass index, kg/m^2	28.3 ± 6.1	27.4 ± 3.9	0.555
Quality of life			
Fatigue Severity Scale (↓)	4.1 ± 1.4	3.8 ± 0.9	0.370
Geriatric Depression Scale (↓)	6.1 ± 3.0	3.7 ± 3.1	0.015[a]

Table 2 Comparison of the baseline characteristics, exercise characteristics, and fitness effects of the intervention between continuous (n = 21) vs interval (n = 22) arm subjects over the first 2 years (randomized segment of the study)

Table 2 Continued

Domain			Continuous	Interval	p
PDQUALIF total score (↓)			47.1 ± 8.7	38.7 ± 9.9	0.005[a]
Cognition					
Executive functions	Inhibition	Flanker–PIS (↓)	25.6 ± 9.1	25.9 ± 9.9	0.939
		Stroop-Interference (↑)	−2.3 ± 5.9	−5.1 ± 7.2	0.189
	Set shifting	TMT B-A, s (↓)	46.7 ± 18.8	59.0 ± 46.3	0.266
		WCST Errors (↓)	34.2 ± 28.3	39.1 ± 21.4	0.532
Verbal memory		AVLT-Recall (↑)	7.4 ± 3.1	9.1 ± 3.8	0.115
Language		COWA (↑)	40.1 ± 13.3	34.7 ± 9.6	0.139
Visuospatial		JLO (↑)	24.0 ± 3.4	23.8 ± 6.0	0.880
		CFT-Copy (↑)	27.4 ± 3.5	28.6 ± 5.2	0.357
Visual memory		CFT-Recall (↑)	13.9 ± 6.1	16.4 ± 7.4	0.228
		BVRT-Error (↓)	6.6 ± 3.9	5.9 ± 3.9	0.528
General		MoCA (↑)	24.7 ± 2.8	24.2 ± 3.0	0.590
Medication					
β-Blocker use, n (%)			3 (14.3)	3 (13.6)	1.000
Exercise					
Setting (individual vs group), n			I = 17, G = 4	I = 17, G = 5	1.000
Dropout for any reason, n (%)			3 (14.3)	5 (22.7)	0.233
Dropout because of study-related AE, n (%)			0 (0)	3 (13.6)	0.196
Exercise characteristics (completers only)					
Attendance, % of required sessions			81.4 ± 15.8	73.0 ± 18.5	0.161
Heart rate		HRX, beats/min	108 ± 14	108 ± 11	0.834
		% of HR_{max}	71.1 ± 7.8	69.2 ± 6.4	0.439
		% of HRR	47.7 ± 10.3	46.6 ± 9.5	0.758
		% of HRAT	100.4 ± 10.7	104.6 ± 11.5	0.270
HRX variability		SD of HRX	6.3 ± 2.6	9.5 ± 2.5	<0.001[a]
Mean walking speed, km/h			4.6 ± 1.1	4.7 ± 1.1	0.786
Effect of intervention					
Aerobic fitness		$\Delta \dot{V}o_2max$	1.1 ± 2.7	2.0 ± 3.5	0.425
Gait speed		Δ7-m walking time	−0.70 ± 1.0	−0.92 ± 1.1	0.551

Abbreviations: ADL = activities of daily living; AE = adverse event; AVLT = Auditory Verbal Learning Test; BP = blood pressure; BVRT = Benton Visual Retention Test; CFT = Complex Figure Test; COWA = Controlled Oral Word Association; G = group; HRAT = heart rate at anaerobic threshold; HR_{max} = maximal heart rate; HRR = heart rate reserve; HRX = heart rate during exercise; HY = Hoehn and Yahr; I = individual; JLO = Judgment of Line Orientation; MoCA = Montreal Cognitive Assessment; PD = Parkinson disease; PDQUALIF = Parkinson's Disease Quality of Life Scale; PIS = percent increase score; TMT B-A = Trail Making Test, subtests B–A; $\dot{V}o_2max$ = maximum oxygen uptake; UPDRS = Unified Parkinson's Disease Rating Scale; WCST = Wisconsin Card Sorting Test.
Values represent mean ± SD unless indicated otherwise. (↓) = lower better; (↑) = higher better.
[a] Significant values.

during the intervention period. Despite theoretical advantages of interval training[18] and group setting,[3] continuous training in individual setting provided equivalent fitness gains with better retention, adherence, and safety. Using continuous electronic heart rate and speed monitoring, we were able to show dose-response relationships in improving aerobic fitness. Similar to community-based studies of self-administered aerobic walking exercise in healthy people,[33] our intervention was conducted in a real-life environment, and is likely to generalize to community dwelling, independently ambulating patients with PD without significant comorbidities.

The Physical Activity Guidelines for Americans by the US Department of Health and Human Services[34] recommend 150 minutes per week of moderate-intensity aerobic physical activity for healthy adults aged 18 to 65 years (Class IA evidence[35]). The mean

Table 3 Efficacy across all completers in various categories

Measure		Pre	Post	p
Aerobic fitness				
$\dot{V}o_2$max, mL/min/kg (↑)		25.4 ± 6.6	27.0 ± 7.0	<0.001[a]
Vital signs				
Systolic BP-supine, mm Hg		132 ± 13	131 ± 13	0.716
Diastolic BP-supine, mm Hg		73 ± 6	73 ± 6	0.842
Pulse-supine, beats/min		66 ± 13	65 ± 11	0.472
Systolic BP-standing, mm Hg		121 ± 17	120 ± 20	0.594
Diastolic BP-standing, mm Hg		72 ± 9	72 ± 10	0.609
Pulse-standing, beats/min		77 ± 12	76 ± 11	0.864
Body mass index, kg/m²		27.3 ± 4.7	27.3 ± 4.7	0.922
Timed motor tests				
7-m Walk time, s (↓)		9.4 ± 1.5	8.7 ± 1.4	<0.001[a]
Right finger tapping (↑)		20.3 ± 4.0	20.4 ± 3.8	0.798
Left finger tapping (↑)		19.1 ± 3.8	19.3 ± 3.6	0.610
Balance				
Functional Reach, in. (↑)		14.8 ± 2.9	14.4 ± 2.9	0.145
UPDRS				
I: Mental, Mood, Behavior (↓)		2.1 ± 1.9	1.6 ± 1.3	0.025[a]
II: ADL (↓)		9.3 ± 4.9	8.8 ± 4.6	0.535
III: Motor (↓)		18.8 ± 10.4	15.9 ± 8.4	0.009[a]
Factors[32]	1 (axial, balance, gait)	4.2 ± 2.4	3.3 ± 2.0	0.002[a]
	2 (rest tremor)	1.4 ± 1.8	1.5 ± 2.1	0.684
	3 (rigidity)	5.9 ± 3.6	4.6 ± 3.1	0.002[a]
	4 (right bradykinesia)	3.8 ± 2.6	3.4 ± 2.2	0.130
	5 (left bradykinesia)	2.8 ± 2.5	2.3 ± 2.3	0.089
	6 (postural tremor)	0.7 ± 0.7	0.7 ± 0.9	0.817
Disability				
Schwab-England Scale (↑)		89.8 ± 7.0	88.9 ± 7.6	0.269
Treatment				
Levodopa preparations, n/(mg/d)		28/(581 ± 283)	29/(619 ± 295)	0.066
Pramipexole, n/(mg/d)		13/(3.1 ± 1.5)	13/(3.2 ± 1.6)	0.785
Ropinirole, n/(mg/d)		12/(11.7 ± 7.1)	13/(10.9 ± 7.2)	0.285
Selegiline, n/(mg/d)		2/(7.5 ± 3.5)	2/(7.5 ± 3.5)	1.000
Rasagiline, n/(mg/d)		8/(1.0 ± 0.0)	9/(1.0 ± 0.0)	0.317
Amantadine, n/(mg/d)		5/(200 ± 71)	5/(200 ± 71)	1.000
Trihexyphenidyl, n/(mg/d)		2/(6 ± 0)	1/(6)	0.317
No treatment, n		4	4	1.000
Levodopa equivalent, mg/d		516 ± 369	550 ± 378	0.057
Diary, h/d				
On time		12.8 ± 4.1	13.7 ± 2.9	0.136
Off time		2.2 ± 2.8	1.8 ± 2.4	0.347
Time with bothersome dyskinesia		0.8 ± 2.2	0.4 ± 1.2	0.185
Sleep time		8.1 ± 1.3	8.3 ± 1.2	0.121

Continued

Table 3 Continued

Measure			Pre	Post	p
Cognition					
Executive functions	Inhibition	Flanker–PIS (↓)	25.5 ± 10.1	22.0 ± 10.2	0.009[a]
		Stroop-Interference (↑)	−4.5 ± 6.3	−3.8 ± 5.3	0.310
	Set shifting	TMT B-A, s (↓)	50.3 ± 35.5	47.5 ± 41.0	0.582
		WCST Errors (↓)	36.0 ± 25.0	37.1 ± 23.9	0.641
Verbal memory		AVLT-Recall (↑)	8.4 ± 3.3	8.5 ± 3.1	0.876
Language		COWA (↑)	37.3 ± 10.9	38.0 ± 13.7	0.663
Visuospatial		JLO (↑)	23.9 ± 4.7	23.6 ± 5.2	0.661
		CFT-Copy (↑)	28.2 ± 4.0	27.5 ± 5.5	0.428
Visual memory		CFT-Recall (↑)	15.9 ± 6.2	16.0 ± 6.0	0.978
		BVRT-Error (↓)	6.0 ± 3.8	6.4 ± 4.2	0.415
General		MoCA (↑)	24.5 ± 3.0	24.8 ± 3.3	0.146
Quality of life, fatigue, depression					
Fatigue Severity Scale (↓)			4.1 ± 1.1	3.6 ± 1.3	0.009[a]
Geriatric Depression Scale (↓)			5.3 ± 3.6	4.5 ± 3.8	0.041[a]
PDQUALIF total score (↓)			41.7 ± 8.9	40.6 ± 9.3	0.071
Subscales		Social role	39.8 ± 13.9	36.6 ± 12.5	0.002[a]
		Self-image/sexuality	43.8 ± 14.0	40.2 ± 14.1	0.006[a]
		Sleep	43.7 ± 17.9	43.7 ± 17.2	1.000
		Outlook	46.2 ± 11.3	43.2 ± 12.4	0.004[a]
		Physical function	43.1 ± 10.9	42.5 ± 11.1	0.621
		Independence	15.7 ± 11.7	14.7 ± 9.6	0.200
		Urinary function	59.4 ± 16.8	63.1 ± 16.7	0.048

Abbreviations: ADL = activities of daily living; AVLT = Auditory Verbal Learning Test; BP = blood pressure; BVRT = Benton Visual Retention Test; CFT = Complex Figure Test; COWA = Controlled Oral Word Association; JLO = Judgment of Line Orientation; MoCA = Montreal Cognitive Assessment; PDQUALIF = Parkinson's Disease Quality of Life Scale; PIS = percent increase score; TMT B-A = Trail Making Test, subtests B-A; V̇o$_2$max = maximum oxygen uptake; UPDRS = Unified Parkinson's Disease Rating Scale; WCST = Wisconsin Card Sorting Test.
Values expressed as mean ± SD. n = 49 for all measures except for V̇o$_2$max and PIS (n = 42). (↓) = lower better; (↑) = higher better.
[a] Significant values.

exercise intensity observed in our study (46.8% [44.0%–49.7%] of the HRR or 69.7% [67.1%–71.8%] of age-predicted HR$_{max}$) is within the limits of moderate-intensity aerobic exercise defined as 40% to 59% of HRR or 64% to 77% of age-predicted HR$_{max}$ by the American College of Sports Medicine.[31] Together with fitness and gait benefits in the "light-intensity aerobic group" (50 minutes per session, 3 times per week, at 40%–50% of HRR) in a recent report,[11] our results suggest that patients with mild to moderate PD can safely exercise per the guidelines for the general adult population and experience benefits.

Improvement in parkinsonism was driven by changes in rigidity and axial functions/gait (accompanied by improvement in gait speed), consistent with the lower extremity predominant nature of the

exercise used in the study. The lack of significant improvements in the activities of daily living scores can be partially attributed to ceiling effects in our highly functional participants. The improvement in the motor UPDRS score (mean = 2.8 points) appears to be meaningful because it exceeded the reported mean minimal clinically important difference of 2.5 (2.3–2.7) points.[36]

The lack of significant changes on most cognitive measures could be attributable to the stability of performance on neuropsychological tests over short time spans in PD with no significant cognitive impairment.[37] However, we observed significant improvement on a measure of inhibition in a magnitude similar to that reported in an aerobic exercise study on healthy elderly.[3] Potential explanations of this selective cognitive improvement include practice

Table 4 Unadjusted and adjusted effect sizes (mean change ± SD) in variables that showed improvement across all completers (n = 49), and n = 42 for V̇o$_2$max and PIS

Outcome	Mean difference ± SD (p value)		
	Unadjusted	Adjusted for levodopa-equivalent only	Adjusted for levodopa-equivalent, year, training mode, setting
V̇o$_2$max, mL/min/kg	1.65 ± 2.90 (<0.001)	1.66 ± 2.90 (<0.001)	1.56 ± 2.74 (<0.001)
7-m Walk, s	−0.66 ± 1.06 (<0.001)	−0.62 ± 1.05 (<0.001)	−0.85 ± 0.94 (<0.001)
UPDRS Motor	−2.88 ± 7.12 (0.007)	−2.75 ± 7.12 (0.002)	−3.37 ± 7.01 (0.002)
UPDRS Mental	−0.51 ± 1.58 (0.029)	−0.52 ± 1.58 (0.025)	−0.97 ± 1.44 (<0.001)
Flanker task–PIS, %	−3.49 ± 8.23 (0.009)	−3.70 ± 8.17 (0.005)	−2.41 ± 7.26 (0.037)
FSS	−0.45 ± 1.16 (0.009)	−0.52 ± 1.13 (0.002)	−0.29 ± 1.09 (0.070)
GDS	−0.78 ± 2.58 (0.041)	−0.77 ± 2.58 (0.043)	−2.09 ± 2.33 (<0.001)
PDQUALIF, total	−1.11 ± 4.21 (0.071)	−1.14 ± 4.21 (0.064)	−1.62 ± 3.95 (0.006)
PDQUALIF subscales			
Social role	−3.17 ± 6.64 (0.002)	−3.51 ± 6.54 (<0.001)	−5.50 ± 6.34 (<0.001)
Self-image/sexuality	−3.62 ± 8.8 (0.006)	−4.26 ± 8.53 (0.001)	−8.30 ± 8.21 (<0.001)
Psychological outlook	−3.06 ± 7.13 (0.004)	−3.73 ± 6.77 (<0.001)	−4.85 ± 6.49 (<0.001)

Abbreviations: FSS = Fatigue Severity Scale; GDS = Geriatric Depression Scale; PDQUALIF = Parkinson's Disease Quality of Life Scale; PIS = percent increase score; UPDRS = Unified Parkinson's Disease Rating Scale; V̇o$_2$max = maximum oxygen uptake.

effect, type I error, or sensitivity of the flanker task performance to changes in aerobic fitness status,[3,23] as suggested by the significant association of decrease in PIS with the increase in V̇o$_2$max in our study.

Fatigue is a multifactorial, common, and disabling feature in PD with no effective treatment.[28] We found an approximately 0.5-point reduction on the FSS, which is considered clinically significant in multiple sclerosis.[38] Aerobic walking may represent an accessible, low-risk supplemental treatment for fatigue and depression, and improve quality of life in PD as in aging, primary depression, cancer, and other chronic medical conditions.[5–7]

Our results suggest that improvement in executive control and average quality-of-life score could be partially explained by increased aerobic fitness, especially in those who tended to have lower fitness at baseline. However, we did not show a direct association of increased aerobic fitness with improvements in parkinsonism, gait speed, mood, and fatigue. Other potential explanations for observed improvements include physical benefits in addition to increased V̇o$_2$max, neuroplasticity,[1,9] practice effects, or the Hawthorne effect.

Without a control group, this phase I/II study cannot prove efficacy, but provides guidance on safety, tolerability, feasibility, and motor and nonmotor effect sizes for a future phase III study on aerobic exercise in PD. Studies on resistance training in PD showed improvements in cognition[16] and parkinsonism.[11,39] Patients with PD also benefit from cognitive training.[40] Future directions and challenges for research on exercise in PD include conducting longer-term and controlled studies, using outcome measures with functional and prognostic relevance, and testing the synergy of different physical training modalities (e.g., aerobic and resistance) or of combined physical and cognitive training.

AUTHOR CONTRIBUTIONS

Ergun Y. Uc: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Kevin C. Doerschug: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Vincent Magnotta: drafting or revising the manuscript for intellectual content. Jeffrey D. Dawson: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Teri R. Thomsen: drafting or revising the manuscript for intellectual content. Joel N. Kline: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Matthew Rizzo, Sara R. Newman, Sonya Mehta, Thomas J. Grabowski, and Joel Bruss: drafting or revising the manuscript for intellectual content. Derek R. Blanchette: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Steven W. Anderson and Michelle W. Voss: drafting or revising the manuscript for intellectual content. Arthur F. Kramer and Warren G. Darling: design or conceptualization of the study, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content.

DISCLOSURE

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This Week's *Neurology*® Podcast

Evaluation and construction of diagnostic criteria for inclusion body myositis (See p. 426)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the July 29, 2014, issue of *Neurology*. In the second segment, Dr. Ted Burns talks with Dr. Steven A. Greenberg about his paper on evaluation and construction of diagnostic criteria for inclusion body myositis. Dr. Adam Numis then reads the e-Pearl of the week about rapid-onset dystonia parkinsonism. In the next part of the podcast, Dr. Alberto Espay focuses part 2 of his interview with Dr. Jon Stone on questions from the audience at Interview Central with regard to his Annual Meeting lecture about functional (psychogenic) disorders in neurology.

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