Exercise in Parkinson's disease: are we narrowing in on the essential elements?

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Mounting evidence supports the benefits of exercise for patients with Parkinson's disease.[1] However, more guidance is necessary from rigorously designed trials to inform the prescription of exercise and optimise outcomes.[2] In *The Lancet Neurology*, Nicolien van der Kolk and colleagues report the results from a single-centre, double-blind, randomised controlled exercise trial (Park-in-Shape) in which the effects of a home-based high-intensity aerobic exercise were compared with a non-aerobic active control intervention in 130 patients with mild Parkinson's disease (Hoehn and Yahr stage ≤2) over 6 months.[3] The aerobic exercise group engaged in stationary cycling (encompassing exergaming—ie, exercise enhanced by gamified elements) at least three times per week for 30–45 min per session, with the target heart rate zone beginning at 50–70% heart rate reserve (HRR) and increasing to a maximum of 80% HRR as fitness increased. The active control group was instructed to do stretching, flexibility, and relaxation exercises three times per week for 30 min per session. Both groups used a tablet-based motivational app and received remote coaching. Results revealed a significant and clinically meaningful difference in favour of aerobic exercise of 4·2 points (95% CI 1·6–6·9; p=0·0020) in the Movement Disorders Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score, measured during a standardised off state (12 h since last dopaminergic medication and, if applicable, deep brain stimulation switched off during measurements). There were no significant differences between groups in any secondary outcomes, with the exception of physical fitness, which was greater in the aerobic exercise group.

Evidence of the benefits of aerobic exercise is converging. A reduction in the risk of Parkinson's disease is associated with moderate to vigorous exercise.[4] Several exercise studies in animal models suggest potential disease-modifying effects of aerobic training.[5] A multicentre, phase 2, randomised controlled trial of 128 patients with de-novo Parkinson's disease (the SPARX trial) revealed a slower rate of decline of the UPDRS motor score in the high-intensity aerobic group (treadmill training) compared with usual care.[6] This difference was statistically and clinically significant. The results of the Park-in-Shape trial[3] strengthen this body of evidence with a rigorous design, including a large sample size, an active exercise control group, and a double-blinded approach—rare in exercise studies.

Collectively, the results of the SPARX and Park-in-Shape trials suggest that high-intensity aerobic exercise three times per week for 6 months has symptom-modifying effects in patients with early Parkinson's disease. These results also suggest that the aerobic nature of the exercise and not the mode of exercise (ie, treadmill walking or cycling) is the crucial ingredient. However, benefits beyond the off-state MDS-UPDRS motor scores should be considered when recommending one mode of exercise over another. The lack of improvement in motor symptoms during the on state in the Park-in-Shape trial suggests the patients might not notice the gains; if functional changes are not apparent, patients will be much less likely to sustain engagement in exercise over the long term. Improvements in walking outcomes in treadmill exercise trials suggest a potential specificity of training effect. Cycling might be a more feasible option for fallers and freezers to engage in high-intensity aerobic exercise safely. However, individuals with freezing and falling are typically categorised as Hoehn and Yahr stage 3 or higher and were not included in this trial. Therefore, generalisability of these results to those with greater disease severity is not known.

Both the SPARX and Park-in-Shape trials included patients with early Parkinson's disease, pointing to a responder group for high-intensity aerobic training—an important initial step. But even within the early Parkinson's disease cohorts, an optimal responder group might have participated. Although both studies were targeting so-called sedentary participants, the inclusion criteria required that patients did not exercise at moderate intensity more than 3 days per week (SPARX) or more than 4 days per week (Park-in-Shape). Therefore, participants might have been exercising regularly before enrolment, albeit less than the dose prescribed in the trials. People who are already engaged in some exercise are more likely to enjoy exercise, volunteer for exercise studies, adhere to the intervention, and subsequently benefit. Future studies should include truly sedentary patients (ie, non-exercisers

or not exercising regularly) to be more representative of the general Parkinson's disease population.

The Park-in-Shape trial included telehealth elements that encompassed remote coaching by a health-care professional, which is important in optimising engagement.[7] Exercise trials using motivational apps with remote coaching by a physical therapist have been shown to improve outcomes in sedentary people with Parkinson's disease.[8] Although telehealth approaches hold promise, numerous regulatory barriers and restrictions from third-party payers in the USA limit the uptake of these approaches. The Park-in-Shape trial reveals the feasibility of integrating telehealth approaches in exercise trials, although more evidence showing feasibility, effectiveness, and cost containment is needed to shift health-care policies further.

In summary, the collective evidence suggests that high-intensity aerobic exercise should be recommended in people with mild Parkinson's disease with the goal of motor symptom modification. Treadmill training or stationary cycling yield similar results related to reducing motor symptoms in the off state but might differentially affect functional outcomes. Patient profile and preferences could guide the choice of aerobic exercise mode to optimise success and sustained adherence. Other forms of exercise should also be considered to improve outcomes beyond the MDS-UPDRS motor scores. Motivational apps and remote coaching might enhance long-term engagement in exercise, although more evidence is needed to isolate the effects of these elements. Additional rigorous and longer-term studies are needed to inform the prescription of exercise programmes with optimised benefits for all patients with Parkinson's disease.

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I declare no competing interests.

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Another sphingosine 1-phosphate receptor modulator for the treatment of patients with multiple sclerosis

The first oral disease-modifying therapy to be approved by regulatory agencies for relapsing forms of multiple sclerosis, fingolimod, has been in use for nearly a decade. Fingolimod is a non-selective sphingosine 1-phosphate receptor modulator that prevents lymphocytes from trafficking out of lymph nodes, thereby reducing relapses and new lesions; it might also have direct effects in the CNS.[1] In the phase 3 clinical trials that led to the approval of fingolimod,[2,3] one of the most concerning short-term risks was transient bradycardia or atrioventricular block in the hours after the medication was started; patients require a first-dose observation to ensure that management is readily available if a clinically relevant change in cardiac conduction occurs. Severe lymphopenia (absolute lymphocyte count $<0{\cdot}2\times10^9$ cells per µL) was reported in the two fingolimod clinical trials supporting regulatory approval in a small proportion of patients receiving the approved 0·5 mg dose,[2,3] although a subsequent publication suggests that this outcome was more common; for example, in one of the trials,[3] 78 (18%) of 425 patients had severe lymphopenia at some point during the study.[4]

A more selective sphingosine 1-phosphate receptor modulator (interacting with subclasses 1 and 5), siponimod, has been approved in the USA for relapsing forms of multiple sclerosis, including active secondary

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