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.

Terry Ellis
Department of Physical Therapy & Athletic Training, Boston University, Boston, MA 02215, USA
tellis@bu.edu

I declare no competing interests.

1 Mak MK, Wong-Yu IS, Shen X, Chung CL. Long-term effects of exercise and physical therapy in people with PD. *Nat Rev Neurol* 2017; **13:** 689–703.
2 Ellis TD, Rochester L. Mobilizing Parkinson's disease: the future of exercise. *J Parkinsons Dis* 2018; **8** (suppl 1)**:** S95–100.
3 van der Kolk NM, de Vries NM, Kessels RPC, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol* 2019; **18:** 998–1008.
4 Fang X, Han D, Cheng Q, et al. Association of levels of physical activity with risk of Parkinson disease: a systematic review and meta-analysis. *JAMA Netw Open* 2018; **1:** e182421.
5 Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol* 2013; **12:** 716–26.
6 Schenkman M, Moore CG, Kohrt WM, et al. Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo Parkinson disease: a phase 2 randomized clinical trial. *JAMA Neurol* 2018; **75:** 219–26.
7 Vassilev I, Rowsell A, Pope C, et al. Assessing the implementability of telehealth interventions for self-management support: a realist review. *Implement Sci* 2015; **10:** 59.
8 Ellis TD, Cavanaugh JT, DeAngelis TR, et al. Comparative effectiveness of mhealth supported exercise compared to exercise alone for people with Parkinson disease: randomized controlled pilot study. *Phys Ther* 2019; **99:** 203–16.

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

Published **Online** September 3, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30333-3
See **Articles** pages 1009 and 1021

progressive multiple sclerosis, on the basis of a small phase 2 trial (n=297) in relapsing-remitting multiple sclerosis and a large phase 3 trial (n=1651) in secondary progressive multiple sclerosis.[5,6] Only those with specific cardiac abnormalities must undergo first-dose observation.[7] Although few participants in the trials developed severe lymphopenia, the phase 2 trial was very short. Of the 29 participants in the 2 mg group who entered the extension phase, two (7%) reported lymphopenia;[8] long-term data from the phase 3 trial have not been published. Patients considering siponimod therapy must have *CYP2C9* genotyping to establish whether they have a contraindicated haplotype or a haplotype necessitating dose adjustment, which complicates the initiation process.

In *The Lancet Neurology*, the results of two phase 3 trials of another oral selective sphingosine 1-phosphate receptor modulator, ozanimod, are presented. Ozanimod also interacts with sphingosine 1-phosphate receptor subclasses 1 and 5. In both studies, adults with relapsing–remitting multiple sclerosis up to age 55 years and with recent inflammatory disease activity were randomly assigned to one of two doses of ozanimod or weekly interferon beta-1a and followed for a mean time on treatment of approximately 13·5 months in the SUNBEAM trial[9] or for 24 months in the RADIANCE trial.[10] The primary outcome in both studies was annualised relapse rate. Patients, who were predominantly white and eastern European, were well matched across groups. In each trial, both target doses of ozanimod (1·0 mg or 0·5 mg daily, after dose escalation) conferred greater reductions in annualised relapse rate than weekly interferon beta-1a. The average overall number of new T2-hyperintense lesions and the average number of active gadolinium-enhancing lesions on the final MRI scan were lower in the ozanimod groups than in the interferon beta-1a groups. Although the trials were not powered to detect a difference in disability outcomes even when the studies were pooled, no difference was apparent in confirmed progression of disability (assessed by the expanded disability status scale) in those treated with ozanimod versus interferon beta-1a.

In both studies, adverse events leading to ozanimod discontinuation were infrequent and less common than in the corresponding interferon group. Four (0·5%) of 873 ozanimod-treated patients (all with baseline heart rate <65) in RADIANCE developed transient, asymptomatic heart rate less than 45 beats per minute, and one RADIANCE participant with baseline dysautonomia had symptomatic reductions in blood pressure and pulse; no patient had a documented heart rate of less than 45 beats per minute in SUNBEAM. Absolute lymphocyte count of less than $0{\cdot}2\times10^9$ cells per L occurred in 18 (4·2%) of 431 patients treated with ozanimod 1·0 mg and four (0·9%) of 438 treated with ozanimod 0·5 mg in RADIANCE, and in 11 (2·5%) of 447 patients treated with ozanimod 1·0 mg (and none of the ozanimod 0·5 mg) participants in SUNBEAM. Infections were rare and not more common in patients who received ozanimod than in those who received interferon beta-1a.

How, if ozanimod is approved for use in multiple sclerosis, will it fit into the burgeoning landscape of sphingosine 1-phosphate receptor modulators or the crowded field of approved disease-modifying therapies? Head-to-head trials of ozanimod with other sphingosine 1-phosphate receptor modulators or with other drugs are unlikely. Although its cost will be relevant, prescribers will almost certainly consider perceived effectiveness versus risks. As with siponimod, ozanimod dose titration at initiation appears to meaningfully reduce cardiac conduction issues, at least in the trial participants who did not have cardiac health issues. If ozanimod attains regulatory approval without requiring universal first-dose observation or *CYP2C9* genotyping, it might improve start-up feasibility, particularly in resource-poor areas. Published data from large sphingosine 1-phosphate receptor modulator trials to date suggest that they are relatively safe with respect to infections in the short term. However, real-world data analysing these and other safety issues in the broader population of patients with multiple sclerosis, in whom risks might be greater because of old age, disability, and long duration of treatment exposure, are needed. It is still unknown whether the much-feared progressive multifocal leucoencephalopathy will occur with siponimod or ozanimod, as it has in the post-marketing era of fingolimod-treated patients.[11] Similar to other disease-modifying therapy studies, the number of non-white people included in the ozanimod trials was negligible, despite the incidence of multiple sclerosis in the USA is now highest in African Americans.[12] Such omissions make it difficult to assess the safety and efficacy of disease-modifying therapies in more racially representative populations.

The therapeutic benefits of fingolimod, siponimod, and ozanimod are thought to be largely mediated by their modulation of sphingosine 1-phosphate receptor subtype 1, inhibiting lymphocyte trafficking and possibly directly targeting neurons. Impacts on oligodendrocytes (via sphingosine 1-phosphate receptor subtype 5) have also been proposed, but although all three therapies do have activity on this subtype, its importance is not known.[1] Ongoing trials of ponesimod, a sphingosine 1-phosphate receptor modulator that acts exclusively on receptor subtype 1,[1] might help to answer this question. Regardless, the results of the SUNBEAM[9] and RADIANCE[10] ozanimod trials provide reassurance about the clinical efficacy and safety outcomes of sphingosine 1-phosphate modulators.

*Ellen M Mowry, *John R Corboy*
Johns Hopkins University, Baltimore, MD, USA (EMM); University of Colorado, Aurora, CO 80045, USA (JRC)
john.corboy@cuanschutz.edu

EMM reports serving as site principal investigator for clinical trials or studies sponsored by Biogen and SunPharma; research support from Sanofi Genzyme and Biogen for investigator-initiated trials; free medication for a clinical trial, of which she is principal investigator, from Teva Neuroscience; and royalties for editorial duties from UpToDate. JRC reports grants from MedDay, Novartis, the Patient Centered Outcomes Research Institute (also as coordinating center), and the National Multiple Sclerosis Society; and personal fees from Mylan, Prime Continuing Medical Education, Medical Logix, and the American Academy of Neurology.

1 Chaudhry BZ, Cohen JA, Conway DS. Sphingosine 1-phosphate receptor modulators for the treatment of multiple sclerosis. *Neurotherapeutics* 2017; **14:** 859–73.
2 Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 402–15.
3 Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 387–401.
4 Kappos L, Cohen J, Collins W, et al. Fingolimod in relapsing multiple sclerosis: an integrated anaylsis of safety findings. *Mult Scler Relat Disord* 2014; **3:** 494–504.
5 Selmaj K, Li DKB, Hartung HP, et al. Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomized, phase 2 study. *Lancet Neurol* 2013; **12:** 756–67.
6 Kappos L, Bar-Or A, Cree BAC. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 study. *Lancet* 2018; **391:** 1263–73.
7 Food and Drug Administration. MAYZENT (siponimod) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209884s000lbl.pdf (accessed June 21, 2019).
8 Kappos L, Li DKB, Stuve O, et al. Safety and efficacy of siponimod (BAF312) in patients with relapsing-remitting multiple sclerosis: dose-blinded, randomized extension of the phase 2 BOLD study. *JAMA Neurol* 2016; **73:** 1089–98.
9 Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *Lancet Neurol* 2019; **18:** 1009–20.
10 Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. *Lancet Neurol* 2019; **18:** 1021–33.
11 Berger JR, Cree BA, Greenberg B, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. *Neurology* 2018; **15:** e1815–21.
12 Wallin MT, Culpepper WJ, Coffman P, et al. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. *Brain* 2012; **135:** 1778–85.

The dawn of robust individualised risk models for dementia

Published **Online**
September 13, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30353-9

See **Articles** page 1034

Mild cognitive impairment (MCI) typically represents a holding pattern for individuals who live for many years without knowing their long-term prognosis. Such uncertainty between improvement or remaining stable versus progressing to a diagnosis of dementia is unsatisfying. Scarcity of specific information or advice compounds this issue. People with MCI do not have access to treatments such as cholinesterase inhibitors or memantine, they usually cannot partake in therapeutic trials, and the absence of a path forward can add to their anxiety and that of family members.[1]

In *The Lancet Neurology*, Ingrid van Maurik and colleagues[2] attempt to clarify this situation. They provide a method for individualised prognosis by indicating which of the participants with MCI in their study were most likely to progress to dementia over 1, 3, and 5 year timeframes. They assessed four separate prognostic models: first, a model incorporating age, sex, and the Mini-Mental State Examination (MMSE); second, a model of age, MMSE, and hippocampal volume; third, a model of MMSE, CSF amyloid β (1–42), and CSF total tau;[3] and fourth, the ATN model[4] of CSF amyloid β (1–42), CSF phosphorylated tau, and hippocampal volume. These models were applied to 2611 MCI participants across the European Medical Information Framework for Alzheimer's disease (EMIF), the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Amsterdam Dementia Cohort (ADC), and the Swedish BioFINDER studies. Of these 2611 MCI participants, 1007 (39%) progressed to dementia within a mean follow-up period of 3 years (SD 2). 808 (80%) participants progressed to dementia due to Alzheimer's disease.

Van Maurik and colleagues had to overcome many difficulties in harmonising the data from so many participants and to ensure that robust and appropriate analyses