The Role of Exercise in Treating Parkinson’s Disease

There is growing evidence that high-intensity exercise is neuroprotective.

By Natalie P. Witek, MD and Cynthia L. Comella, MD

Parkinson’s disease (PD) is a progressive neurodegenerative disorder marked by rigidity, tremor, and gait instability. There is no cure or medication known to alter the underlying disease mechanism of PD. As PD progresses, there is associated disability. Nonmotor features (eg, cognitive impairment, depression, apathy, and autonomic nervous system dysfunction) may be the most disabling features. Complications of therapy, including motor fluctuations, dyskinesia, and hallucinations, can become more prominent as the disease progresses. For some, the advancing disease leads to institutionalization in nursing homes. Patients with PD who have falls, gait instability, or dementia are twice as likely as their counterparts without these features to be placed in a nursing home. Medical advances, such as the introduction of levodopa therapy, have changed the life expectancy of patients with PD, but this and other medications often result in side effects and long-term complications, such as dyskinesias and motor fluctuations. Although there are many medications to treat the symptoms and complications of PD, currently there are none that can reverse or slow the neurodegenerative process leading to disability in PD.

Excessive Exercise and Prevention

There is growing evidence that exercise, particularly vigorous exercise, may provide neuroprotective effects that can improve motor function, cognition, and quality of life in patients with PD. Exercise is now considered a treatment of PD with multiple benefits and few adverse effects.

Animal and prospective cohort studies provide evidence that vigorous exercise may exert neuroprotective effects and decrease the risk of developing PD. There have been several cohort studies suggesting that regular exercise during the midlife period reduces the risk for PD years later. Meta-analysis of prospective studies affirms the diminished risk of developing PD following moderate to vigorous physical activities in preceding years. An analysis of 2 prospective cohort studies that included 48,574 men and 77,254 women showed a 60% reduced risk of PD in men who performed at least 10 months of strenuous exercise per year compared to those who regularly exercised less than 2 months per year. Similarly, the results of the prospective Cancer Prevention Study II Nutrition Cohort, which followed over 140,000 participants from 1992 and 2001, showed that those who underwent moderate to vigorous exercise had 40% lower risk of PD than those who did not.

While these results are promising, it is difficult to ascertain if patients with preclinical PD had an aversion to exercise earlier in life. Nearly 40% of patients who have had PD for 10 years are not exercising. However, there is a growing body of evidence to suggest that exercise clinically improves symptoms of PD, has neuroprotective effects, and should be recommended to patients with PD.

Molecular Mechanisms for the Benefits of Exercise

Animal studies suggest several different mechanisms in which exercise leads to neuroprotective effects and promotes neuroplasticity. Neuroplasticity, defined as the ability of neuronal circuits to make structural and functional adaptive changes, can be induced by exercise and effect the nigrostriatal and related motor circuits that are involved in the pathophysiology of PD. Endurance exercises promote neurogenesis and neuroprotection in animals. Several studies have shown that exercise exerts neuroprotective effects against dopaminergic neurotoxins 6-hydroxydopamine (6-OH-DA) and 1-methyl-4-phenyl,1,2,3,6-tetrahydropyridine (MPTP). In a transgenic mouse model of diffuse Lewy body disease, mice that exercised for 3 months had significantly less α-synuclein aggregation than in the brains of sedentary mice. These findings suggest that in animal models of PD, exercise has neuroprotective effects.

General animal models show that exercise influences cognition through a number of ways. Vigorous exercise induces expression of brain neurotrophic factors, including brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF). Elevated expression of
BDNF appears to be a key factor mediating the effects of exercise on cognition. BDNF is a protein that easily crosses the blood–brain barrier, is widely distributed throughout the brain, and increases in proportion to exercise intensity. Exercise also induces expression of insulin-like growth factor 1, which interacts with BDNF and protects against neurotoxic insults to the hippocampus.\(^3\)

Exercise has been shown to increase dendritic length and complexity and dendritic spine density within the hippocampus. Exercise increases expression of genes associated with neuroplasticity and downregulates genes linked to oxidative stress.\(^3\) In a study involving a transgenic mouse model of Alzheimer’s disease (AD), 5 months of exercise significantly reduced brain amyloid concentrations.\(^3,14\) These changes are associated with improved performance in spatial memory and object recognition.\(^3\)

**Motor Function Improvements From Exercise**

Exercise improves gait speed and motor symptoms (eg, bradykinesia) and decreases falls in patients with PD. Evidence supports that specific walking programs and other high-intensity aerobic and nonaerobic training programs provide superior improvements in walking speed and gait parameters compared to programs aimed at promoting flexibility, relaxation, and low-intensity physical activity.\(^15-18\) In a single-blind randomized controlled trial, 67 patients with early-stage PD (Hoehn & Yahr scale [HY] 1-3) were assigned to groups doing stretching and resistance exercise, lower-intensity supervised treadmill training, and higher-intensity treadmill training 3 times a week for 3 months. Patients in treadmill-training groups had improvement of their walking speed and distance, along with improvement of their cardiovascular fitness, based on maximal oxygen consumption (peak VO\(_2\)). Motor function was evaluated using the Unified Parkinson’s Disease Rating Scale (UPDRS) Part-III motor examination and manual dexterity assessments. In the UPDRS, higher scores equate to worse motor symptoms. The resistance group was the only group to show improvement in strength and was interestingly the only group to show mild improvement in the UPDRS motor subscale (−3.5; \(P < .05\)).\(^9\) The study in PD and exercise (SPARX) randomized sedentary patients with recently diagnosed PD (HY 1 and 2) to either high-intensity exercise, defined as 80% to 85% of maximum heart rate for 4 days per week; moderate-intensity exercise, defined as 60% to 65% of maximum heart rate for 4 days per week; or usual care for 6 months. There was significantly less decline in motor scores based on UPDRS in those assigned to the high-intensity group compared to the moderate-intensity treadmill training group. Patients in the high-intensity group experienced mean change of only 0.3 (95% CI, −1.7 to 2.3) on the UPDRS, whereas patients in the moderate-intensity group had scores that worsened by 3.2 (95% CI, 1.4 to 5.1; \(P = .03\)) at 6 months.\(^9\) This study also showed that patients with PD are able to comply with a high-intensity exercise program 3 times per week for 6 months without significant adverse effects.

Other exercise modalities have also been shown to improve specific motor functions in patients with PD. Cycling for 3 months improved gait in sedentary patients with PD.\(^19,20\) Forced exercise of the lower extremities during tandem cycling resulted in improvements both in global and fine motor function.\(^21\) Progressive resistance exercise training consisting of weight-bearing exercises 2 times per week for 24 months showed that long-term supervised exercise improved bradykinesia, overall motor scores, and general functional performance in patients with PD at a 24-month follow-up.\(^22\) A comparison of tai chi to stretching or strength training 2 times per week for 3 months demonstrated that tai chi reduced the incidence of falls. Compared to stretching, tai chi also improved UPDRS scores at 6-month follow-up (−5.02; 95% CI, −6.90 to −3.13, \(P < .001\)).\(^16\) Various exercise modalities improve motor symptoms or delay worsening of symptoms in PD, and there is no clear single method that is superior.

**Impact of Exercise on Cognition**

Currently, there are no approved pharmacologic therapies that alter disease outcomes for patients with PD and mild cognitive impairment (MCI) or PD dementia (PDD). The prevalence of cognitive impairment in PD varies, but some estimate that up to 30% of patients with PD have cognitive impairment at initial presentation.\(^23\) Exercise has been shown to have beneficial effects on cognition in the general population. Aging is associated with progressive reduction of gray matter volume, whereas exercise and cardiovascular fitness are associated with greater cortical gray matter and hippocampal volume.\(^3\) Prospective studies have shown increased cortical gray matter or hippocampal volumes in seniors randomized to 6 to 12 months of exercise compared to less active controls.\(^3\) Likewise, blood volume of the hippocampal dentate gyrus was increased at the end of a 3-month exercise program, which correlated with aerobic fitness defined by peak VO\(_2\).\(^3\) In addition, there is less brain atrophy in patients with AD who are cardiovascularly fit.\(^3\) These studies suggest that improved cardiovascular fitness preserves brain tissue in regions vital for memory and cognition.

A meta-analysis of 29 randomized controlled trials involving 2,049 subjects assessed the impact of aerobic training on neuropsychological performance and showed that aerobic exercise produced modest improvements in attention, speed, executive function, and memory among adults without dementia.\(^24\) Studies that assessed longer interventions were associated with improved attention and processing speed.\(^24\) One of the longest trials analyzed cognitive outcomes of patients who underwent supervised progressive resistance exercise training for 24 months and showed improved working memory and...
attention in patients with mild-to-moderate PD. Similarly, a systematic review found global cognitive function, processing speed, sustained attention, and mental flexibility strengthened in patients with PD who participated in exercise programs.

Interventions that improve cognitive function in patients with PD range from adapted tango, cognitive training (Nintendo Wii Fit) combined with motor training, treadmill training, progressive resistance-exercise training, and a combination of balance and strengthening exercises. Aerobic exercise improved cognition in the acute and longer-term follow-up periods. Treadmill training performed for approximately 60 minutes 3 times per week over a period of 24 weeks produced large improvements in cognition in patients with mild-stage PD. The effect was more robust in patients assigned to the more intensive exercise regimen. Another study found that at 18 months follow-up, patients over age 50 with subjective memory impairment who participated in moderate-intensity aerobic exercise during 50-minute sessions 3 times per week for 6 months experienced modest improvement in cognitive memory, language, and praxis tests based on the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog). Various modalities of exercise improve cognition in patients with PD, and the improvements in cognition can be observed in both the immediate and long-term periods.

Impact of Exercise on Quality of Life
Among patients with PD, exercise is associated with an improved quality of life. In a 24-week supervised treadmill training exercise, the frequency and severity of motor and nonmotor symptoms, and subsequent effects on daily living improved at follow-up for patients with PD. In addition, a positive effect on mood and depression was observed, as indicated by a decrease in Beck Depression Inventory scores after 6 months of training. Progressive resistance exercise by patients with PD for 2 days each week for 24 months resulted in improved quality of life based on Parkinson’s Disease Questionnaire-39 scores. A systematic review of the effect of physical activity on nonmotor symptoms in PD reviewing 20 studies of various exercise modalities with intervention time frames ranging from 4 weeks to 3 years showed that exercise improved depression and daytime sleepiness in patients with PD.

Exercise has been associated with the amelioration of numerous nonmotor symptoms leading to improvement of quality of life.

Obstacles to Exercise and Limitations in Current Literature
Although there have been a number of studies showing the benefits of various forms of exercise, most do not address long-term follow-up and adherence to exercise regimens. Reported reasons for failure to participate in training sessions include scheduling issues, commuting challenges, medical comorbidities, hospitalizations, motor vehicle accidents, musculoskeletal injury, and family demands. Depression, difficulty initiating movement, and decreased motivation are nonmotor symptoms of PD that also impede patients from initiating exercise.

The long-term effects of exercise in patients with PD are limited, as most prospective interventional studies are short, ranging from 1 to 6 months. Most studies lack adequate control groups and have small sample sizes and poor follow-up regarding long-term outcomes and adherence to the studied interventions. Most of the studied interventions utilized some form of supervision. Practically, the cost of physical therapy and personal trainers may prohibit patients from participating in supervised exercise. Adherence to and benefits from self-initiated independent exercise that is typically encouraged by clinicians remains unknown.

Recommendations
Exercise leads to well-established general health benefits, including improvement of cerebrovascular health and psychological well-being in addition to reduction of osteoporosis/fracture risk, age-related muscle loss, and risk of malignancy. Patients with PD stand to gain specific benefits in improving motor symptoms and cognition and have fewer falls following exercise regimens. All patients with PD should be encouraged to exercise.

The Office of Disease Prevention and Health Promotion recently released the 2018 Scientific Report, which recommends that older individuals should participate in moderate-intensity activities for 150 to 300 minutes per week, which is similar to the recommendations of the Centers for Disease Control and Prevention (CDC). Examples of moderate-intensity activity include walking briskly (3 to 4 mph), mopping, vacuuming, or raking a yard. The CDC states that adult patients, including those more than 65 years of age need at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity (jogging or running) every week combined with muscle strengthening on 2 or more days each week.

These recommendations also apply to patients with PD, who may also benefit from additional supervision, especially when they are just beginning to exercise after having been relatively sedentary. The Physical Activity Guidelines Advisory Committee acknowledges that some activity is better than none, and that appreciable benefits accrue from regular physical activity below the targeted range. Patients should be encouraged to engage in any physical activity that they are willing to perform. However, it is important to differentiate exercise (ie, repeated physical activity that elevates the heart rate) from lower levels of activity (eg, light housework).

We recommend that at each patient encounter, patients be provided specific recommendations and be reminded to exercise. If time or circumstances do not allow for discussion, a printed list of recommendations may be provided to each patient.
Box. Recommendations for Exercise for Patients With Parkinson’s Disease

Progressive muscle-strengthening activities for at least 2 days each week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders, and arms)

**Plus**

Moderate-intensity exercise 150-300 minutes each week. (Examples: walking briskly [3 to 4 mph], mopping or vacuuming, or raking a yard.)

Or

Vigorous-intensity aerobic exercise for at least 75 minutes each week, if the patient is able to participate. This may provide more benefits than moderate-intensity exercise. (Examples: jogging, bicycling, or lap swimming.)

Notes

If the patient has not been exercising regularly, he or she may benefit from a physical therapist or physical trainer to direct initial exercise.

Patients should not be discouraged if they do not meet targeted exercise recommendations. Some exercise is better than no exercise.

It is best to encourage an exercise activity the patient enjoys, and that will motivate him or her to participate in regular physical activity.

NOTE: These recommendations are based on collective review of the list recommendations from the CDC (2018), United States Office of Disease Prevention and Health Promotion (2018), and the AAN recommendations on Counseling Patients with Parkinson Disease About Regular Exercise Regimen. (2015). 29-31


Natalie P. Witek, MD
Movement Disorder Fellow
Rush Parkinson’s Disease and Movement Disorders Program
Rush University Hospital
Chicago, IL

Cynthia L. Comella, MD
Professor of Neurology
Rush Parkinson’s Disease and Movement Disorders Program
Rush University Hospital
Chicago, IL

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