MAYO CLINIC

Aerobic Exercise: Evidence for a Direct Brain Effect to Slow Parkinson Disease Progression

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Abstract

No medications are proven to slow the progression of Parkinson disease (PD). Of special concern with longer-standing PD is cognitive decline, as well as motor symptoms unresponsive to dopamine replacement therapy. Not fully recognized is the substantial accumulating evidence that long-term aerobic exercise may attenuate PD progression. Randomized controlled trial proof will not be forthcoming due to many complicating methodological factors. However, extensive and diverse avenues of scientific investigation converge to argue that aerobic exercise and cardiovascular fitness directly influence cerebral mechanisms mediating PD progression. To objectively assess the evidence for a PD exercise benefit, a comprehensive PubMed literature search was conducted, with an unbiased focus on exercise influences on parkinsonism, cognition, brain structure, and brain function. This aggregate literature provides a compelling argument for regular aerobic-type exercise and cardiovascular fitness attenuating PD progression.

 ■ Mayo Clin Proc. 2018;93(3):360-372

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Parkinson disease (PD) is a relatively common neurologic condition with perhaps 1 million affected people in the United States. Increasingly, their treatment is falling into the hands of primary care physicians, who should be able to provide optimal care to most patients.[1-3] As previously described,[2] appropriate carbidopa/levodopa administration is the single most crucial medication strategy. Herein, the argument is advanced that the other important component of optimal PD treatment is engagement in regular aerobic-type exercise. Although no medications are proven to slow PD progression, there is substantial evidence for vigorous exercise attenuating PD progression, which is the specific focus of this article.

Exercise advice may be skeptically viewed by patients. The lay public is bombarded by health advice, some biologically supported and some that is arbitrary, unsupported, or commercially driven. Exercise is easily dismissed as yet another dictum from health experts. Moreover, regular exercise implies strenuous, time-consuming physical work, which for some people is novel. Thus, an exercise prescription for people with PD is easily discarded, especially in the absence of definite proof.

IMPEDIMENTS TO CLINICAL TRIAL ASSESSMENT OF PD EXERCISE INFLUENCES

Definitive arguments for any health intervention are expected to come from clinical randomized controlled trials (RCTs). The outcome of interest is preventing the slow neurologic decline that occurs with PD. Unfortunately, a valid and reliable RCT of long-term exercise to slow PD progression is not truly feasible for several reasons.

First, PD progression tends to be very slow. Reliable and valid biomarkers of PD progression have yet to be developed. Assessment requires outcome measures that will not be contaminated by medication effects (ie, levodopa and related drugs); this precludes motor outcomes routinely used in PD clinical trials (eg, Unified Parkinson Disease Rating Scale scores). From a patient's perspective, the most important markers of clinical progression are dementia and levodopa-refractory symptoms, which are measureable and not subject to medication influences. However, these problems typically do not develop for many years or decades and, thus, are not amenable to RCTs.

Second is the physical and motivational challenge of longer-term engagement in an

Mayo Clin Proc. ■ March 2018;93(3):360-372 ■ https://doi.org/10.1016/j.mayocp.2017.12.015
www.mayoclinicproceedings.org ■ © 2017 Mayo Foundation for Medical Education and Research

aerobic exercise program. Long-term adherence to a rigorous exercise protocol among senior patients with PD is potentially problematic.

Third, confirmation of exercise effort in such a clinical trial is not easily assessed, although cardiovascular fitness is an objective outcome of long-term aerobic exercise. Not to be overlooked in such clinical trials is off-protocol exercise in the "sedentary" control patients cognizant of the study hypothesis that exercise may slow PD progression.

THE RATIONALE FOR THIS REVIEW

Definitive proof of exercise slowing PD progression is unlikely to be forthcoming from RCTs because of the previously mentioned methodological problems. However, there is a very extensive and diverse literature relating to direct exercise influences in the brain, relevant to PD. At an elementary level, this includes exercise-induced brain neuroplasticity, maintenance of synaptic connections, and preservation of brain integrity. Macroscopically, exercise influences on brain integrity are now measureable with modern brain magnetic imaging technology.

The goal of this article is to review the evidence for long-term aerobic-type exercise as a means for slowing PD progression. Although exercise is well-recognized to attenuate brain atherosclerotic risks (ie, cerebrovascular disease), this focus will be on direct brain influences of aerobic-type exercise. Because subject reviews tend to have agendas that may bias interpretation, a concerted effort was made to survey the entire published literature identified in a PubMed search and report both positive and negative findings. The intent is to provide clinicians with the evidence needed for counseling their patients with PD.

METHODS: LITERATURE SEARCH

This PubMed literature search was performed using 2 search term strategies: *exercise and Parkinson disease* and *exercise and cognition. Cognition* was chosen because cognitive impairment/dementia is perhaps the most feared outcome of patients with PD. All the titles from this literature search to January 15, 2017, were reviewed, and relevant papers were read. Mixed results and negative trials are cited in this review. The reference list contains all the relevant papers; however, individual studies are not separately addressed when included in cited meta-analyses.

Included in this review are adult human (age >18 years) and animal studies. Aerobic-type exercise was the focus because a preliminary reading of this literature indicated that this is the most robust and comprehensive component of this exercise literature. It also allowed extension to animal studies, where running exercise is a common experimental variable. Although resistance exercise might be relevant to this topic, preliminary review of resistance exercise publications suggested too few articles and too varied methods to reliably assess. Papers reporting exercise outcomes in nonrelevant disease groups were excluded (eg, patients with diabetes, cancer, etc). Only studies of long-term exercise were included, excluding short-term exercise trials. Studies using outcome measures that could be influenced by symptomatic drug treatment were excluded (eg, carbidopa/levodopa for PD). The PubMed search targeting *exercise and Parkinson disease* yielded 1781 titles; *exercise and cognition* yielded 5054 titles.

ARTICLE HIGHLIGHTS

- Parkinson disease is a slowly progressive neurodegenerative condition; after many years, dementia or medication-refractory motor symptoms may develop.
- A myriad of animal studies document a direct, favorable effect of aerobic-type exercise on the brain; this includes liberation of neurotrophic hormones and enhancement of a variety of neuroplasticity mechanisms. Exercise tends to protect animals from neurotoxins that induce parkinsonism.
- Long-term exercise and fitness in healthy humans is associated with greater volumes of cerebral cortex and hippocampus and less age-related white matter pathology.
- Midlife exercise is associated with a significantly reduced later risk of Parkinson disease.
- Conclusion from this evidence: Regular aerobic-type exercise tending to lead to fitness is the single strategy with compelling evidence for slowing Parkinson disease progression. All patients with Parkinson disease should be encouraged to engage in regular such exercise.

RESULTS: ANIMAL STUDIES

Exercise Facilitates Neuroplasticity in Animals

Much of the early literature relevant to this topic was from animal studies, which provided the initial scientific rationale for exercise directly enhancing brain neuroplasticity. The term *neuroplasticity* implies the ongoing capacity of the brain to form and modify synaptic connections. This is the basis for motor and cognitive memory and is the fundamental repair and maintenance process tending to counter neurodegenerative disease and brain aging.

Exercised Animals Perform Better on Simple Cognitive Tests. Controlled trials of running exercise in rats and mice use running wheels or treadmills. Many such studies have documented significant exercise-related improvement in spatial memory (maze) or object recognition.[4-17] Exercised monkeys (1 hour daily of treadmill exercise for 5 months) performed better than sedentary control monkeys.[18]

Microscopic and Neurophysiologic Evidence of Exercise-Related Neuroplasticity. The hippocampus is crucial to memory and is one of the very few brain regions where new neurons are generated: neurogenesis. Many published studies in rats/mice have consistently documented enhanced hippocampal neurogenesis associated with long-term running exercise.[9,11,14,19-28] The putative neurophysiologic substrate of memory is hippocampal long-term-potentiation, which was significantly enhanced by running exercise in rodents,[13,15,23] although only in male and not female rats in 1 study.[29] Learning involves restructuring of synaptic connections, and several rodent studies documented enhanced dendritic length and complexity and increased dendritic spines after long-term running exercise.[7,21,30-32]

Exercise Facilitates Biochemical Markers of Neuroplasticity. Long-term running exercise in rodents increased brain factors known to mediate neuroplasticity, including CREB and intracellular kinases.[5,10,33,34] Long-term running exercise also enhanced the expression of synaptic plasticity genes[35] and synaptic proteins such as synapsin I and synaptophysin.[7,17,32,36,37]

Exercise Influences on Brain Neurotrophic Factors

Neurotrophic factors have long been proposed as a potential therapeutic target for neurodegenerative diseases, including PD.[38,39] Applied in vitro, they enhance neuron vitality, survival, and neuritic outgrowth; they tend to protect neurons from biologic insults (neurotoxins).[39,40] Intuitively, enhanced brain neurotrophic factor concentrations should benefit neurodegenerative disease, ie, PD.

Brain Neurotrophic Factor Levels Increase With Exercise in Animals. Perhaps the most studied neuroplasticity factor is brain-derived neurotrophic factor (BDNF). Many animal studies have documented significantly increased brain BDNF levels with exercise.[4-6,9,10,12-14,17,19,23,26,33,36,37,41-44] Brain insulin-like growth factor I interacts with BDNF and increases with exercise.[8]

Glial cell line—derived neurotrophic factor (GDNF) caught the attention of PD researchers when it was recognized to promote the survival and differentiation of dopaminergic neurons in vitro.[45] It attenuates neurotoxin-induced parkinsonism in rodents.[46] Several studies have reported increased brain concentrations of GDNF in animals exercised long-term.[47-49]

Animal Models of Neurotoxin-Induced Parkinsonism, Attenuated by Exercise

Parkinson disease symptoms are primarily mediated by neurodegeneration of the dopaminergic nigrostriatal system, and dopamine replenishment with levodopa therapy is the most efficacious symptomatic treatment. Although PD is not simply a dopamine disorder, selective neurotoxin-induced destruction of the dopaminergic nigrostriatal system has been used as a treatment model. This is done with either nigrostriatal infusion of 6-hydroxydopamine (6-OH-DA) or systemic administration of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). Rodent studies using these neurotoxins have assessed possible neuroprotective effects of exercise.

Mayo Clin Proc. ■ March 2018;93(3):360-372 ■ https://doi.org/10.1016/j.mayocp.2017.12.015
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Exercise Increases Neurotrophic Factor Levels and Attenuates 6-OH-DA Nigrostriatal Neurotoxicity. Multiple studies in rodents have reported that the parkinsonian motor deficits from unilateral nigrostriatal injection of 6-OH-DA are markedly attenuated or reversed by exercise,[44,49-55] although with 3 negative trials.[56-58] In this unilateral condition, forced use of the affected limb also attenuated the deficit (cast immobilization of the unaffected limb).[47,59] Conversely, preventing use of the 6-OH-DA–affected limb by casting exacerbated the motor deficit.[60] In these studies, postmortem histologic analysis documented partial restoration of histologic markers of striatal dopaminergic terminals[20,49-51,53-55,59-62] or neurons,[20,49,62] although not confirmed in 1 study.[52] In controlled studies, daily exercise in 6-OH-DA animals increased striatal BDNF and GDNF levels[49] or BDNF levels,[42,53,55] postulated as relevant to the neuroprotective outcomes. Forced overuse of a limb before 6-OH-DA injection elevated striatal GDNF levels, attenuated the motor deficit, and reduced the striatal dopamine loss.[47]

Exercise Tends to Reduce MPTP Nigrostriatal Neurotoxicity. Mice systemically injected with MPTP develop bilateral parkinsonism due to selective neurotoxic destruction of the dopaminergic nigrostriatal system. Exercise attenuated MPTP-induced parkinsonism in 7 studies,[48,54,63-67] but not in 2 others.[68,69] Cast immobilization exacerbated the motor deficit.[70]

Histochemical markers of the dopaminergic nigrostriatal system were inconsistently protected in these studies. Evidence of preserved or restored (sprouted) dopaminergic terminals were found in the minority of investigations,[48,54,65,70] with 7 of 11 reports documenting no change in the dopaminergic terminal markers.[63,68,69,71-74] Midbrain dopaminergic neuron counts were partially preserved with exercise in most,[48,64,66,75] but not all,[67,73] studies. A dose-effect was documented in 2 investigations,[64,75] with greater exercise duration and intensity associated with incremental attenuation of parkinsonism and histochemical results.

In other MPTP studies, exercise attenuated postsynaptic changes caused by loss of dopaminergic input to striatal neurons. Specifically, exercise reversed striatal neuron hyperexcitability[76] and tended to restore glutamate (AMPA) receptors[77] and dendritic spine density.[31]

RESULTS: HUMAN STUDIES

Humans and Neurotrophic Factors

As cited previously herein, animal studies have consistently documented increased brain concentrations of neurotrophic factors with long-term exercise (eg, BDNF, GDNF). Neurotrophic factors are proposed as neuroprotective for neurodegenerative disease (ie, PD).

Exercise Increases BDNF in Humans. Brain-derived neurotrophic factor is a small molecule and crosses the blood-brain barrier.[78,79] Hence, circulating BDNF concentrations should correlate with brain levels in humans. Most studies in normal humans have documented increased serum BDNF concentrations, both after acute exercise and with long-term exercise, as summarized in a recent meta-analysis.[80]

Exercise Increases Serum BDNF in Patients With PD. Serum BDNF levels significantly increased after 1 month of treadmill exercise in a cohort of patients with PD; the levels were unchanged in the unexercised control patients with PD.[81] In 2 other uncontrolled studies, 8 weeks of cycling exercise significantly increased serum BDNF levels.[82,83] Perhaps relevant is the finding that low serum BDNF concentrations were significantly associated with reduced cognitive scores in a cohort of patients with PD.[84]

Side Story: Direct Brain Administration of GDNF in Patients With PD. As mentioned previously herein, the neurotrophic factor GDNF protects dopaminergic neurons and promotes their survival in vitro[45]; in vivo, it attenuates the neurotoxic effects in animal models of parkinsonism.[46] However, unlike BDNF, the large GDNF molecule does not cross the blood-brain barrier, and blood levels are independent of brain concentrations.

Laboratory studies documenting neurotrophic effects of GDNF on dopaminergic neurons were the basis for brain infusion trials in patients with PD. Because GDNF does not

cross the blood-brain barrier it was administered via cannulas implanted in the brains (striata) of patients with PD.[38,46] Trials of these direct infusions yielded mixed results. An initial open-label trial revealed parkinsonian benefit, but this was not replicated in an RCT.[85] The failure in the controlled trial was possibly attributed to the limited distribution or poor retrograde neuronal transport of GDNF from the striatal injection site; this large molecule diffuses poorly in brain tissue.[38]

Exercise and PD

Midlife Exercise Reduces Later PD Risk. In a meta-analysis of prospective studies, midlife exercise conferred a significantly lower subsequent risk of developing PD.[86] Subsequently, this outcome was similarly reported in 2 individual large cohorts[87,88] and in 1 cross-sectional analysis.[89] Obviously, reverse causation cannot be excluded; ie, before PD, patients might have been less inclined to exercise due to subclinical PD-related factors.

Exercise in Early PD and Later Dementia. No clinical trials have assessed whether exercise in early PD reduces later risks of dementia. This would be a difficult investigation for the reasons discussed at the beginning of this article. However, limited studies suggest favorable trends.

In a cross-sectional study involving 2252 patients with PD, questionnaire-based regular exercise was associated with less cognitive decline after 1 year.[90] Again, reverse causation could have explained this finding (ie, those with more severe PD may have been disinclined to exercise).

Numerous small trials assessing 1 to 6 months of aerobic-type exercise by patients with PD have documented statistically significant cognitive improvement; however, the outcomes have been modest, limited, or inconsistent across cognitive measures. Most of these studies included a nonexercise control group,[91-96] but 2 were uncontrolled[97,98] and 2 others assessed only 1 or 2 patients with PD.[99,100]

Non-PD Human Clinical Studies: Exercise and Cognition

Although studies addressing exercise and cognition in PD are limited, there is a substantial literature relating to exercise influences on cognition in the general population. Note, however, that exercise-related cognitive enhancement in healthy adults may be limited by a ceiling effect and may fundamentally differ from biological mechanisms counteracting a very slow PD neurodegenerative process.

Prospective Exercise Trials in Healthy Adults: Limited Cognitive Benefits. Numerous clinical trials have assessed cognitive outcomes after several months of aerobic-type exercise in healthy adults. In the aggregate, the benefits have been modest and inconsistent. These findings may be summarized as follows.

The first of several meta-analyses assessed 16 prospective RCTs of 1 to 18 months of aerobic-type exercise and documented significant, but modest cognitive benefit in healthy adults (some seniors).[101] In contrast, 2 subsequent meta-analyses of prospective RCTs of long-term exercise in healthy seniors revealed no aggregate benefit.[102,103] Subsequently, 6 of 8 individual RCTs assessing long-term aerobic-type exercise documented significant cognitive improvement[104-109]; the 2 negative studies assessed 1 to 2 years of regular walking.[110,111] Complicating interpretation of these findings is uncertain exercise engagement in the exercise group. Even when attendance is monitored, there is no assurance that vigorous and persistent exercise is performed. Moreover, off-protocol exercise in the sedentary control groups is never monitored.

Recent cross-sectional exercise studies in seniors have also generated inconsistent cognitive findings. On the one hand, better cognitive scores were associated with greater physical activity, either questionnaire based[112,113] or tabulated by a 6-day accelerometer assessment.[114] In contrast, 2 decades of high-effort endurance exercise reported by older adults documented no cognitive differences compared with a nonsedentary control group of similar age.[115]

Some of the limitations of the prospective exercise trials may be better addressed when the independent variable is fitness, which is the intended outcome of aerobic exercise. Fitness can be physiologically defined by the measured oxygen uptake during maximum exercise. There is a voluminous literature

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relating to fitness and cognition, with compelling evidence favoring fitness.

Fitness Is Associated With Better Cognition in Healthy Adults. Several large studies measured fitness at baseline and assessed later cognitive outcomes. The largest of these studied 1.2 million Swedish men aged 18 years inducted into the military.[116] Fitness was measured at the time of induction, revealing highly significant positive correlations between cardiovascular fitness and cognitive test scores; the findings were similar when the assessment was confined to the 1432 monozygotic twins among their inductees. Also, in this cohort, fitness at age 18 years predicted educational outcomes 10 to 36 years later,[116] whereas lower fitness was associated with a greater risk of dementia, with follow-up to 42 years.[117] Similar outcomes were documented in 2 community-based studies. In the first study, baseline fitness predicted cognition 25 years later[118]; in the other, baseline fitness was associated with slower cognitive decline over decades of aging.[119] In a cohort of military veterans, better baseline fitness predicted a significantly lower risk of cognitive impairment at mean follow-up of 10 years.[120] Several cross-sectional studies have reported that better fitness was concurrently associated with better cognitive scores,[121-125] although in another study, this was found only in seniors and not in young adults.[126] Masters athletes performed significantly better on 2 of 4 cognitive tests than sedentary control subjects.[127]

One recent publication cautions about reverse causation in these fitness studies, arguing that early socioeconomic or inherited advantages may confer both healthier lifestyles and better cognition; or, that those with better cognition tend to choose healthier lifestyles.[128]

Regular Exercise Reduces the Risk of Later Dementia, Cognitive Decline. Meta-analyses of midlife-documented exercise/physical activity found a significantly reduced frequency of later cognitive decline[129] and dementia.[130] More recent similar prospective studies have reported similar significant outcomes,[131-134] although this trend in 1 other study was only marginally significant.[135] Midlife vigorous leisure activity (ie, more vigorous than walking) was associated with a significantly lower risk of a death certificate diagnosis of dementia at 29 years of follow-up.[136]

Cross-sectional studies found midlife fitness to be associated with a reduced risk of later dementia,[137] and higher reported lifetime physical activity was associated with better cognitive scores.[113] Multiple studies have found midlife exercise to be linked to a reduced risk of later mild cognitive impairment,[116,138-145] which is recognized to be a frequent prelude to dementia.

Established Dementia/Mild Cognitive Impairment: Aerobic-Type Exercise Generally Provides Cognitive Benefits. Among those already cognitively impaired, most prospective exercise trials documented significant cognitive benefits[146-155]; however, a few reported only modest outcomes,[156-158] with 1 negative study.[159] The most recent meta-analysis assessing RCTs of aerobic exercise in demented patients reported significant positive effects on cognition.[160] Although 2 earlier meta-analyses of long-term exercise in demented patients were negative, they included numerous trials using nonaerobic interventions.[161,162]

Aerobic-Type Exercise Favorably Influences Brain Volumes, Integrity, and Connectivity

Parkinson disease is a brain neurodegenerative condition that is most likely to develop in middle age and beyond. Note that normal aging is associated with brain atrophy and attrition, apparent on routine brain magnetic resonance imaging (MRI). Advances in brain MRI software allow precise measurement of neuroanatomical features, as well as brain activation and connectivity. In this era of advanced brain MRI technology, clinical trial evidence has documented that long-term aerobic exercise tends to induce favorable changes in brain structure and function, paralleling cognitive benefits.

Fitness and Exercise Are Associated With Hippocampus Volumes. The hippocampus is a crucial component of brain memory circuits. Hippocampal atrophy is not only a marker of Alzheimer disease but also is found in PD with dementia.[163,164] In cross-sectional analyses controlling for relevant variables,

larger hippocampal volumes were significantly associated with cardiovascular fitness.[124,165] The volume of the entorhinal cortex (which encompasses the hippocampus) was similarly correlated with fitness, at least on 1 side.[166]

In prospective RCTs, hippocampal volumes increased with 1 to 2 years of aerobic exercise.[167,168] Likewise, in a shorter treadmill exercise RCT (3 months), hippocampal volumes were significantly larger in proportion to the measured change in fitness.[169]

Fitness and Exercise Are Associated With Neocortical (Gray Matter) Volumes. In the Framingham Heart Study, poor fitness at age 40 years was associated with a smaller overall brain volume 20 years later.[170] Several studies documented that physically fit seniors have significantly less age-related cortical volume loss.[121,123,171,172]

Prospective 6-month RCTs of exercise documented increased neocortical volumes in 2 studies,[173,174] but not in 1 walking exercise trial.[175] Reported physical activity has concurrently been associated with greater gray matter volumes,[176,177] whereas reported walking distances prospectively correlated with cortical volumes 9 years later.[178]

Fitness Is Associated With White Matter Integrity. Diffusion tensor imaging (DTI) MRI measures white matter integrity and microstructure. One DTI measure of white matter health is fractional anisotropy, with high values indicating greater microstructural integrity. Among seniors, fitness was associated with greater brain DTI fractional anisotropy,[179-182] and in 1 study fitness correlated with fractional anisotropy measured 5 years later.[183] Seniors who improved fitness after 1 year of walking exercise improved brain white matter fractional anisotropy.[111] Estimated physical activity in advanced seniors (mean age, 87 years) was associated with higher DTI fractional anisotropy.[184]

Brain White Matter Hyperintensities (Leukoariosis) Are Less With Fitness. Normal aging is variably associated with white matter hyperintensities (leukoariosis). These lesions are thought to reduce brain reserve and at least mildly contribute to deficits from neurodegenerative disease. Increased fitness is associated with reduced volumes of these white matter hyperintensities (ie, less leukoariosis),[185,186] although in 1 study this significant relationship was found only in men.[187] Masters athletes had 83% less leukoariosis volume compared with a matched sedentary control group.[188]

Functional-MRI: Brain Activation and Connections Improvement With Exercise. Brain functional MRI (fMRI) assesses cortical activation and connectivity during cognitive tasks. In healthy seniors, aerobic fitness has been associated with better fMRI connectivity and cortical activation compared with unfit seniors.[122,189,190] Prospective (6-12 months) exercise in healthy seniors improved fMRI cortical connectivity and activation in cognitive networks.[189,191]

fMRI Brain Activation and Connectivity Improved With Exercise in PD. In patients with PD, brain fMRI connectivity declines with progressing PD and correlates with cognitive decline.[192] A prospective, 3-month cycling exercise trial in patients with PD revealed increased brain activation in several relevant nuclei.[193] In another fMRI study in exercising patients with PD, long-term cycle pedaling rates strongly correlated with improved thalamus-cortex connectivity.[194]

SYNOPSIS

An initial rationale for considering exercise to slow PD progression came from animal studies, where long-term running exercise consistently improved cognitive outcomes, increased brain neurotrophic factor concentrations, enhanced biomarkers and microscopic evidence of neuroplasticity, and attenuated neurotoxin-induced parkinsonism. These findings suggested a direct beneficial effect of exercise on the brain, relevant to PD.

In patients with PD, as well as healthy adults, exercise increased BDNF levels. In prospective studies, midlife exercise consistently has been associated with a reduced later risk of PD.

Progression to dementia is the most feared PD complication, but it does not lend itself to clinical trial assessment of exercise influence. However, adults without PD who engage in

Mayo Clin Proc. ■ March 2018;93(3):360-372 ■ https://doi.org/10.1016/j.mayocp.2017.12.015
www.mayoclinicproceedings.org

midlife exercise have significantly reduced subsequent risks of dementia and mild cognitive impairment. Cardiovascular fitness in midlife is associated with better cognition many years later. Finally, brain volumes (hippocampus, neocortex), brain connectivity and activation, and white matter integrity are significantly favored by exercise and fitness.

ADVICE TO PATIENTS

If regular exercise slows PD progression, what exercise(s) to choose? In animal studies, the focus was on running exercise because this is what rats and mice voluntarily will do. Extrapolating from that to humans suggests that aerobic-type exercises, in general, may accomplish similar outcomes. This is corroborated by the many studies documenting associations between cardiovascular fitness (the outcome of long-term aerobic exercise) and favorable cognitive outcomes, greater brain volumes, brain connectivity, and white matter integrity. This literature would suggest that any exercise routine that potentially leads to fitness should be appropriate. Thus, not only running may serve this purpose, but also countless aerobic routines that tend to increase heart rate, induce perspiration, and generate fatigue. This includes many exercise routines that can be done by those with gait problems or arthritic lower limb joints.

Unfortunately, there are no investigations that provide insight into the ideal exercise duration. Perhaps the American Heart Association exercise guidelines[195,196] are a good starting point when advising patients: "…moderate-intensity aerobic physical activity for a minimum of 30 minutes on five days each week or vigorous-intensity aerobic activity for a minimum of 20 minutes on three days each week." That guideline also advises resistance exercises "for a minimum of two days each week." However, it seems reasonable to direct patients to gradually increase exercise intensity and duration to improve fitness.

Whereas this literature suggests that fitness, per se, is neuroprotective, this may not be sufficient if not maintained by ongoing exercise. Note that the cited animal literature suggests that exercise triggers brain surges of neurotrophic hormones and induction of neuroplasticity mechanisms. Will these abate if exercise is not maintained? Will the fit patient with PD who abandons exercise still benefit? Because this is unresolved, it would be appropriate to counsel continued engagement in exercise regardless of baseline fitness.

The evidence for exercise favoring PD progression has implications for carbidopa/levodopa treatment. Engagement in vigorous exercise by those with PD usually requires an appropriately optimized levodopa treatment program. Arbitrarily delayed or underdosed levodopa treatment compromises both the ability and motivation to exercise. Carbidopa/levodopa may be deferred in those who can remain active, and whose quality of life is not substantially affected by PD symptoms. However, there is nothing to be gained by the admonition to defer or limit carbidopa/levodopa in the hope of "saving it for later." Carbidopa/levodopa treatment guidelines have previously been clearly delineated and should be easily adopted by primary care physicians.[1-3]

CONCLUSION

No medications are proven to slow the progression of PD. After years of living with PD, patients develop symptoms that do not have a dopamine substrate and do not benefit from dopamine replacement, notably, dementia and levodopa-refractory motor symptoms. However, evidence from many avenues of scientific investigation argues for ongoing aerobic exercise as a means to slow PD progression. This should be routine advice to patients with PD.

Abbreviations and Acronyms: **BDNF** = brain-derived neurotrophic factor; **DTI** = diffusion tensor imaging; **fMRI** = functional magnetic resonance imaging; **GDNF** = glial cell line–derived neurotrophic factor; **MRI** = magnetic resonance imaging; **MPTP** = 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; **PD** = Parkinson disease; **RCT** = randomized controlled trial; **6-OH-DA** = 6-hydroxydopamine

Potential Competing Interests: The authors report no competing interests.

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