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ARTICLE *in* NATURE REVIEWS NEUROLOGY · JULY 2011

Impact Factor: 15.36 · DOI: 10.1038/nrneurol.2011.107 · Source: PubMed

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OPINION

How might physical activity benefit patients with Parkinson disease?

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Abstract | Parkinson disease (PD) is a neurodegenerative disorder characterized by progressive motor and nonmotor impairments. These impairments incline many patients towards a sedentary lifestyle, which has many deleterious consequences. Accumulating evidence suggests that patients with PD might benefit from physical activity and exercise in a number of ways, from general improvements in health to disease-specific effects and, potentially, disease-modifying effects (suggested by animal data). Many issues remain to be addressed, including the need to perform clinical trials to demonstrate these presumed benefits of physical activity and exercise in patients with PD. These trials must also address safety issues, such as an increased risk of falls and cardiovascular complications in more-active patients. Identifying ways to induce a sustained behavioral change, using specifically tailored programs that address potential barriers such as depression, apathy and postural instability, may lead to an improved quality of life in individuals with PD.

Speelman, A. D. *et al. Nat. Rev. Neurol.* **7**, 528–534 (2011); published online 12 July 2011; corrected online 16 August 2011; doi:10.1038/nrneurol.2011.107

Introduction

Parkinson disease (PD) is a neurodegenerative condition characterized by progressive motor symptoms, including gait disturbances and balance instability. Patients with PD can also develop a range of nonmotor complications, such as depression, apathy, sleep disturbances, constipation, and cognitive dysfunction. Together, these motor and nonmotor impairments might encourage the individual to adopt a sedentary lifestyle.[1,2] This response creates a vicious circle, because physical inactivity can negatively affect several clinical domains of PD (Figure 1).

A sedentary lifestyle may represent more than just a consequence of PD; it could reflect a deliberate compensatory strategy to prevent further complications, observed, for example, in patients with severe postural instability who try to avoid falls by staying indoors. Indeed, fear of falling is common in patients with PD, and might result in a reduction in their outdoor physical activities.[3] The positive effect of exercise on the healthy human brain has been studied extensively (Box 1) but evidence demonstrating the benefits of physical activity specifically in patients with PD is limited. Throughout this article, 'exercise' refers to planned physical activity undertaken specifically to maintain or improve physical fitness and functional capacity.[4,5] Participation in exercise, as well as normal daily physical activities, results in improved physical fitness in healthy individuals as well as those with PD. This state of well-being carries a low risk of premature health problems, and provides the individual with energy to participate in an extended range of physical activities.[5]

In this Perspectives article, we extrapolate from data on healthy populations, and evidence from clinical trials in patients with PD or other neurological conditions, to present and explore 10 potential reasons why an active lifestyle might benefit patients with PD (Box 2). Possible risks associated with increased physical activity in patients with PD are also discussed, along with the imminent challenges that must be addressed to achieve a sustained active lifestyle for this group of patients.

Competing interests
The authors declare no competing interests.

Potential benefits of exercise

Improving cognitive function

Cognitive impairment is common in individuals in the advanced stages of PD (up to 80% of patients will eventually develop dementia),[6] and findings from the past 5–6 years suggest that cognitive decline actually begins early in the course of disease.[7] Only two small studies have investigated the benefits of an aerobic exercise program on cognitive dysfunction in patients with PD.[8,9] One of these studies investigated the effects of a multimodal physical exercise program in 20 patients with PD. The participants were assigned to either an intervention group (who received general physical training for 6 months) or a control group. The results showed a beneficial effect of training on executive function.[8] The other study evaluated the benefits of exercise in 28 patients with PD, who were allocated to either an intervention program of twice-weekly exercise for 12 weeks or a control group. The researchers concluded that exercise had selective benefits on cognitive functioning by improving frontal-lobe-based executive function.[9] Additional evidence from studies in elderly individuals and patients with Alzheimer disease suggests that exercise may postpone cognitive deterioration[10] and delay the onset of dementia.[11] The aerobic component of exercise, in particular, drives these clinical effects.[12] These promising results should now be explored further in large trials of exercise in patients with PD.

Arrest of osteoporosis

The prevalence of osteoporosis is high in patients with PD: up to 63% of women with PD and 20% of men with PD have this condition.[13,14] By comparison, in age-matched healthy populations the prevalence of osteoporosis is 29% in women and 12% in men.[15] Several factors might contribute to accelerated bone loss in patients with PD, such as physical inactivity, vitamin D deficiency, muscle weakness, low body weight, and hyperhomocysteinemia. Most of these factors evolve during the course of PD and reinforce each other. Patients with PD also have a high risk of falling[3] which, in combination with osteoporosis or osteopenia, increases the risk of fall-related fractures.[16] Prevention or reduction of osteoporosis

would, therefore, be of great benefit for individuals with PD.

Conversely, physical activity and exercise are associated with improved bone health.[17] Although the optimal training method for stimulating bone growth in adults has not yet been defined, evidence points to a combination of high-impact activities, such as jumping, and weight-bearing exercises such as sprinting, jogging or stair climbing.[18] Whether patients with PD can improve their bone health by adapting to a physically active lifestyle, or by following an exercise program, remains to be demonstrated in appropriately designed studies. The high-impact exercises required to examine this effect may not be suitable for all patients, owing to their high risk of falls; less-hazardous weight-bearing exercises, such as regular walking, aerobics or dancing, may be more appropriate for patients with PD.

Preventing cardiovascular events

The precise incidence of cardiovascular events, such as myocardial infarction or cerebrovascular disease, is unclear in patients with PD. In general, cardiovascular risk factors (including diabetes, a history of smoking, hypertension, and high cholesterol levels) are less common in patients with PD than in controls.[19] A review suggested that patients with PD might have an increased propensity to develop comorbid cerebrovascular complications,[20] but more work is needed to confirm this association.

A sedentary lifestyle is one of the leading causes of death among individuals in the general population.[21] In addition, the amount of physical activity is inversely related to all-cause mortality.[21] In particular, exercise training positively influences cardiovascular risk factors and reduces the incidence of cardiovascular disease (including cerebrovascular events).[22] The American College of Sports Medicine and the British Association of Sports and Exercise Sciences recommend, therefore, that all healthy adults aged between 18 and 65 years should regularly participate in physical activity to promote and maintain health.[23,24] Prospective studies suggest that adherence to this recommendation is associated with reductions of 20–30% in the risk of cardiovascular disease.[25] The general benefits of physical activity and exercise can also be expected to apply to individuals with PD; however, such effects remain to be demonstrated in this population. In terms of intrinsic capacity to engage in exercise, studies have shown that the maximal oxygen uptake of patients with PD was no different from that of controls, but men with PD reached their maximal oxygen uptake earlier than did controls, suggesting less mechanical efficiency of movement during exercise, perhaps due to their muscle rigidity.[26] This earlier saturation of maximal oxygen consumption indicates that patients with PD must stop exercising earlier than controls.

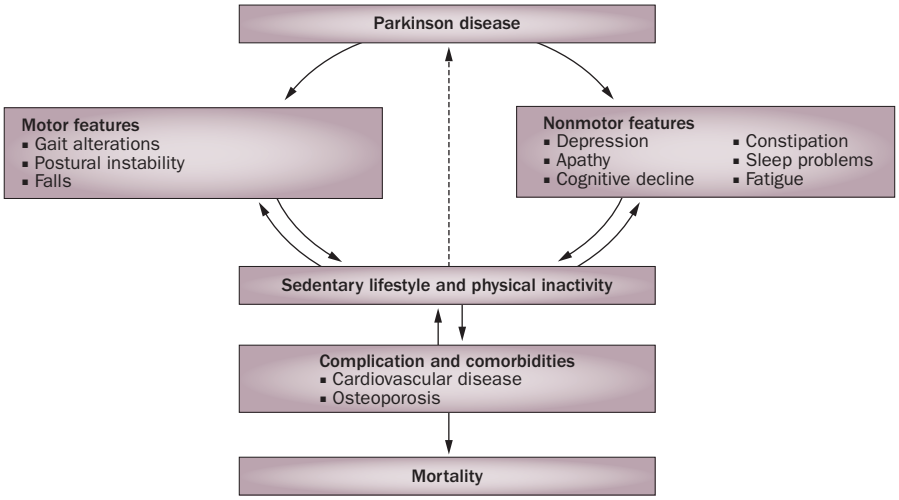

Figure 1 | The vicious circle of physical inactivity in PD. Patients with PD tend to lead a sedentary lifestyle, owing to a combination of motor and nonmotor features. A sedentary lifestyle has various adverse effects (solid arrows): secondary worsening of PD-related symptoms and signs (for example, constipation can worsen because of physical inactivity); development or worsening of comorbidities and complications (such as cardiovascular disease); and increased mortality risk. In addition, by extrapolation from studies in rodents with experimentally induced parkinsonism we speculate that a sedentary lifestyle could negatively influence the course of PD itself (dotted arrow). Abbreviation: PD, Parkinson disease.

Box 1 | The effects of exercise on the human brain

The beneficial effects of physical activity on brain functions in healthy people presumably work via adaptive neuroplasticity—the brain's capacity to adjust through dynamic neuronal reorganization.[4] Studies in healthy older rodents have shown that regular aerobic activity triggers plasticity-related changes in the CNS, including synaptogenesis, enhanced glucose utilization, angiogenesis, and neurogenesis.[67] In older adults who are free of cognitive impairment, aerobic exercise promotes brain health by reducing inflammation, suppressing oxidative stress, and stabilizing calcium homeostasis.[68] Furthermore, release of endogenous neurotrophins (such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, and galanin) during regular aerobic exercise is associated with synaptic plasticity and enhanced cognitive performance, learning and memory.[69,70]

Several imaging studies have underpinned the beneficial cerebral effects of exercise in humans. For example, aerobic fitness increased the volume of gray and white matter in sedentary people.[71] Furthermore, increased physical activity (achieved via cognitive behavioral therapy) produced an increase in gray matter volume in patients with chronic fatigue syndrome.[72] Currently, no data are available as to whether exercise can induce structural or functional brain alterations in patients with Parkinson disease, and at what level potential neuroplastic changes might occur. Adaptive neuroplasticity can occur spontaneously in patients with Parkinson disease, at the level of both the basal ganglia and the cortex,[73] and such compensatory processes may even start in the preclinical phase.[74] Studies to determine whether exercise can drive or facilitate these processes should be high on the research agenda.

Preventing depression

The relationship between physical activity and mental health has been widely investigated in populations without PD. A systematic review of 11 randomized controlled trials concluded that exercise is an effective treatment for depression in healthy individuals,[27] although the underlying mechanisms remain poorly understood.

Depression is a common neuropsychiatric symptom associated with PD. The prevalence of depression depends on the patient's age and the severity of their motor symptoms, increasing from 15.6% in Hoehn and Yahr stages I–II, to 47.9% in stages IV–V.[28] Several studies have also examined the effect of a physical activity intervention on depression in patients with PD. One study

Box 2 | Potential benefits of exercise

The 10 possible benefits of exercise in patients with Parkinson disease are as follows:

- Prevention of cardiovascular complications
- Arrest of osteoporosis
- Improved cognitive function
- Prevention of depression
- Improved sleep
- Decreased constipation
- Decreased fatigue
- Improved functional motor performance
- Improved drug efficacy
- Optimization of the dopaminergic system

reported a statistically significant improvement in depression in the group who had received the intervention, as compared with a group with no intervention or a massage group,[29] whereas other studies reported no clear improvement in depression with exercise.[8,30–32] The reader should note that depression has mostly been included as an exploratory outcome in studies involving patients with PD. Large clinical trials are needed to examine the benefit of physical exercise specifically on depression in this population.

Improved sleep

Sleep dysfunction occurs in two-thirds of patients with PD, among whom the most common problem is frequent night-time awakening.[33] In a small, non-controlled study of 20 patients with PD, some indication of sleep improvement was seen in those who participated in 36 group sessions of aerobic exercises and muscular strengthening.[34] In the general population, sedentary elderly individuals with moderate to severe sleep dysfunction showed improvements (assessed by the Pittsburgh Sleep Quality Index) in sleep-onset latency and sleep duration after moderate-intensity exercise.[35] To assume that exercise could also improve sleep-related disorders in patients with PD seems reasonable; however, this area clearly needs to be studied in more detail.

Decreased constipation

Constipation is the most common gastrointestinal symptom in individuals with PD, and is reported by 50–80% of patients.[36] Although the causes of constipation in patients with PD are multifactorial, this symptom is in part attributable to a lack of physical exercise.[37] No studies have yet evaluated the influence of exercise or increased physical activity on constipation in patients with PD; however, we might reasonably expect that patients with PD would experience similar benefits to those seen in healthy individuals, in whom cross-sectional studies have shown an inverse relationship between physical activity and the risk of constipation.[38] The mechanisms underlying the positive effect of exercise on constipation are unclear, but could include increased colonic motility, decreased blood flow to the gut, biomechanical stimulation of the gut during bouncing movements (such as running) or compression of the colon by abdominal musculature, and increased fiber intake as a result of increased energy expenditure.[38]

Decreased fatigue

Fatigue is experienced by 30–50% of patients with PD;[39] in a community-based population study, 44.2% of 233 patients with PD reported fatigue, compared with 18% of 100 age-matched controls.[40] Longitudinal studies in the general population showed that the amount of physical activity undertaken was inversely correlated with the presence of fatigue.[41] This pattern was also apparent in patients with PD.[41] Results obtained from studies in patients with chronic fatigue syndrome showed that cognitive behavioral training effectively reduced fatigue; however, changes in physical activity did not reduce levels of fatigue.[42]

A review of nine randomized controlled trials found encouraging evidence that patients with chronic fatigue syndrome benefit from exercise therapy, but also concluded that more studies are needed.[43] If these findings can be extrapolated to patients with PD, exercise training in patients with PD might be useful to avoid or reduce fatigue in this population, although no data have been obtained from clinical trials to support this hypothesis. The other side of the coin is that exercise may paradoxically increase fatigue, so future trials should tailor the level of exercise to each patient's individual capacity.

Improved motor performance

Individuals with PD invariably experience functional decline in a number of motor domains, including posture, balance, gait, and transfers (such as moving between a bed and chair). Several studies, including systematic reviews and a meta-analysis, have evaluated the effects of exercise on these functional deficits (Table 1). The overall conclusions of these studies were that exercise can improve physical functioning, health-related quality of life, leg strength, balance, posture, gait, and physical condition. The data showing that exercise improves functional motor performance in patients with PD seem robust; however, the question remains as to which exercise protocol is best suited to individual patients.

Improved levodopa efficacy

Several studies[44–47] have investigated the association between exercise and the pharmacokinetics of levodopa, one of the drugs most commonly used to treat the symptoms of PD. Levodopa is transported to the brain and converted to dopamine, which ameliorates the dopamine deficit that occurs in patients with PD. Although most studies have found no effect of exercise on the efficacy of levodopa,[45,47] one report revealed a trend towards improved absorption of this drug during physical activity.[47] In theory, exercise might stimulate levodopa absorption because of accelerated gastric passage or increased mesenteric blood flow.[47] Alternatively, levodopa might cross the blood–brain barrier more efficiently, due to higher blood pressure and heart rate during exercise.[48] However, these studies only evaluated a single, brief bout of exercise (maximum 2 h). Clearly, further studies are needed, particularly of prolonged exercise interventions, to assess the effect of exercise on the response to levodopa therapy in individuals with PD.

Optimized dopaminergic signaling

Exercise could potentially influence endogenous production and release of dopamine in patients with PD, leading to enhanced dopaminergic neurotransmission.[49] This postulated mechanism is in line with behavioral studies that reported a positive effect of endurance exercise on both simple and more-complex movements in patients with PD, both of which were executed faster after exercise.[50] Although no concurrent neuroimaging studies were performed, the authors speculated that this improved performance could be attributed to augmented synthesis and release of dopamine and other catecholamines in the prefrontal cortex, nucleus accumbens and basal ganglia.[51] However, some researchers have expressed concern that, when exercising, the motor response of PD patients may be pushed towards normal values and the motor system might use up the available levodopa faster, leading to a greater (or earlier) dopamine shortage in the hours following exercise. This hypothesis needs to be studied in detail.

Table 1 | Summary of published reviews on the effect of exercise on motor disablility in PD

Review	Topic	Number of:		Criteria for inclusion	Conclusions
		Studies	Patients		
Goodwin *et al.* (2008)[32]*	Exercise or physical activity	14 RCTs	495 patients with PD	An exercise or physical activity intervention compared with any comparator Outcomes included physical performance or functioning, falls and/or HRQOL	Exercise is effective at improving physical functioning, HRQOL, leg strength, balance and walking Insufficient evidence that exercise improves falls and depression
Crizzle *et al.* (2006)[63]	Physical or therapeutic exercise	7 studies (including 3 RCTs)	438 patients with PD	Interventions comprising physical or therapeutic exercise Effects of physical exercise were evaluated Published in a peer-reviewed journal	Patients improve physical performance and activities of daily living through exercise
Keus *et al.* (2007)[64]	Physical therapy	29 studies (including 23 RCTs)	Not applicable	Physical therapy Only trials with sufficient data Core areas of physical therapy Published in English, Dutch or German	Four specific recommendations: cueing strategies to improve gait; cognitive movement strategies to improve transfer; exercises to improve balance; and training of joint mobility and muscle power to improve physical capacity
Kwakkel *et al.* (2007)[65]	Physical therapy	23 RCTs	1,063 patients with PD	Core areas of physical therapy Published in English, German or Dutch	Evidence in favor of specific task-oriented exercise training to improve posture, balance control, gait and gait-related activities, and physical condition
Mehrholz *et al.* (2010)[66]*	Exercise	8 RCTs	203 patients with PD‡	Treadmill training versus no treadmill training	Patients who receive treadmill training are more likely than those who do not receive this training to show relief of gait hypokinesia

*Meta-analysis. ‡UK Brain Bank criteria. Abbreviations: HRQOL, health-related quality of life; PD, Parkinson disease; RCT, randomized controlled trial.

Prevention of PD

The preceding section dealt with how exercise might improve motor and nonmotor dysfunction in patients who have clinically overt PD. However, the fascinating possibility exists that physical activity or exercise could also postpone the onset of parkinsonism, or perhaps even prevent disease manifestations altogether, in asymptomatic individuals who are predisposed to develop the disease. This issue is all the more pertinent because we are starting to identify people who are at an increased risk of developing PD: individuals with rapid eye movement sleep behavior disorder; family members (of individuals with PD) who have a reduced sense of smell; people with chronic constipation; or those who carry a mutation in a PD susceptibility gene.[51]

The holy grail in the field of PD is to reliably identify these individuals as early as possible and to expose them to treatments that might slow down, or even arrest, the underlying disease process that will ultimately result in parkinsonism. Although such pre-emptive treatments are not yet available, we may logically assume that exercise could prove to be an intervention. This idea is further supported by epidemiological studies that investigated the relationship between physical activity and the risk of subsequently developing PD, and by studies in mouse models of PD that have highlighted the neuroprotective and neurorestorative effects of exercise.[52] However, whether the association between exercise and risk of PD can be explained by a truly preventive effect of exercise on the development of PD, or by a decrease in baseline recreational activity as a result of preclinical PD, is not yet clear.[53]

Risks of exercise in PD

Individuals with PD have an increased risk of falls and fall-related injuries, such as fractures.[2,3] The rates of falls and injuries might increase still further if these patients are stimulated to become more active, as even in the general population physically active adults have a higher incidence of leisure-time and sport-related injuries than their less-active counterparts.[23] In patients with PD, fall rates seem to taper off in the end stages of the disease, as the patients become progressively less mobile.[3]

Paradoxically, although exercise may increase the likelihood of falls in individuals with PD, it could also reduce the overall risk associated with falls and the associated fractures; for example, by improving strength, fitness, bone density or overall balance.[54] One study investigated the effects of a home-based exercise program in patients with PD.[46] The results suggested that this intervention tended to reduce the incidence of fall events and injurious falls.[55] Additional evidence came from the RESCUE study—a large, multicenter study of rhythmic somatosensory cueing, in which a vibrating cylinder attached to the wrist was used to improve gait in patients with PD.[56] The researchers reported that the intervention led to improved mobility without an increased risk of falls.[56] The case as to whether exercise increases the patient's risk of falling is, therefore, far from closed; moreover, this issue should be considered in future trials.

Exercise is also associated with an increased risk of cardiovascular complications. Although the risk of sudden cardiac arrest or myocardial infarction is very low in generally healthy adults during activities of moderate intensity, the risk of these events increases during vigorous physical activity, especially in sedentary individuals or those with pre-existing coronary artery disease.[23] Nonetheless, physically active or aerobically fit individuals enjoy a 25–50% reduction in their lifetime overall risk of developing cardiovascular disease.[23] Comparable data are not available for patients with PD, but they are unlikely to be an exception to this general rule. However, the risk of comorbid cerebrovascular disease seems to be higher in patients with PD than in the general population.[20] This increased risk is likely to be ameliorated by exercise, because regular moderate exercise has been shown to be a protective factor for development of cerebrovascular disease.[20]

Other potential adverse effects of exercise include increased fatigue and levodopa requirements, as discussed earlier.

Changing sedentary lifestyles

Regular physical activity is commonly accepted to be an important component of a healthy lifestyle. However, simply informing people about the health benefits of physical activity is not enough to attain a sustained behavioral change, which might explain why so many citizens (not just patients with PD) lead a sedentary life. Inducing a lasting change in exercise behaviors offers a particularly great challenge for patients with neurological disorders. In patients with PD, several specific barriers to such changes exist—not only the motor disabilities (gait and balance problems), but also the diverse nonmotor problems (cognitive decline, apathy, and depression). The progressive nature of these symptoms provides reasons to doubt whether patients with PD can be motivated to remain active in the long term.

If a true behavioral change can be attained in patients with PD, they might need specific coaching and counseling (rather than the general advice given to healthy adults). Evidence shows that effective physical activity interventions in this group should incorporate behavioral change principles.[57] Social cognitive theories propose that the control of behavior is based on two types of expectations: self-efficacy (individuals' belief in their ability to perform actions to attain a desired outcome) and outcome expectations (the belief that a certain consequence will be produced by personal action).[58] To change lifestyle and attain an enduring behavioral shift might, therefore, call for specific strategies tailored to the individual's preferences and needs. These behavioral programs should focus on appropriate supervision and social support from spouses and caregivers.[59,60] Our research group has begun to address these issues in the ParkFit study (Box 3).

Further research is needed to develop combined counseling and exercise programs for patients with PD, which focus on a behavioral change and have long-term follow-up. So far, the available studies have had no postintervention exercise-free period, and only short-term follow-up.[61,62] Extended follow-up is important to evaluate whether the beneficial effects of exercise persist, and whether a reduced-intensity maintenance exercise program is needed to uphold the effects. Other studies should try to separate symptomatic effects from potential disease-modifying effects.

Conclusions

Compelling theoretical reasons support the avoidance of a sedentary lifestyle and the promotion of physical activity (including muscle strengthening, aerobic exercise and weight-bearing exercise) for people with, or at risk of developing, PD. Currently, however, we lack adequate knowledge about the merits of exercise specifically in patients with PD. The best available evidence stems from studies in healthy individuals or patients with other neurodegenerative diseases, which suggest a beneficial effect of exercise on cardiovascular mortality or morbidity[21] and on cognitive dysfunction[10,11] or mood.[27] Animal studies have raised the fascinating possibility that exercise might exert a neuroprotective effect in experimentally induced parkinsonism (Box 4) but these findings have yet to be translated to the human disease.

Development of a reliable strategy to stimulate an active lifestyle in patients with PD will be essential, and these efforts must pay careful attention to safety issues and each patient's individual capacities. Such exercise programs must also consider various barriers that could impede an active lifestyle specifically in patients with PD, such as apathy, fatigue, depression and cognitive dysfunction. The primary aim of these approaches is to induce a sustained behavioral change, with the hope of providing symptomatic relief of both motor and nonmotor disability,

Box 3 | The ParkFit study

Our research group designed the ParkFit program—a multifaceted intervention to promote physical activity in sedentary patients with Parkinson disease. This intervention is being studied in the ParkFit trial, which will investigate whether this program affords increased levels of physical activity that persist for 2 years.[75] The trial will also evaluate the possible health benefits and risks of increased physical activity.[75]

The ParkFit trial is a multicenter randomized controlled trial that will compare two different exercise interventions: physical therapy with a specific emphasis on promoting a physically active lifestyle (the ParkFit program); and matched physical therapy with a specific emphasis on the safety and quality of performing daily activities (the ParkSafe program). The ParkFit program emphasizes behavioral change, using a combination of accepted motivational techniques and strategies, and personal health coaches to induce a lasting increase in exercise behavior for patients with Parkinson disease. The ParkFit program incorporates several specific elements: an educational workbook (including a health contract and logbook) designed to educate the patient about the benefits of physical activity, provide advice about suitable activities, help to identify and overcome perceived barriers to engagement in physical activity, and provide information on recruiting social support; a personal activity coach; goal setting; ambulatory monitoring with visual feedback; and physical therapy. The first results of the trial are expected by the end of 2011.

Box 4 | Evidence from animal studies

In rodent models of Parkinson disease, which rely on administration of neurotoxins (6-OHDA or MPTP) to induce parkinsonian symptoms, exercise attenuates the degree of injury to midbrain dopaminergic neurons, and restores basal ganglia function through adaptive mechanisms of dopamine and glutamate neurotransmission.[76–79]

In rats, voluntary or forced exercise (on a running wheel or treadmill) initiated before or during the administration of 6-OHDA and continued for an additional 1–5 weeks afterwards leads to the preservation of neurons in the substantia nigra pars compacta and to the attenuation of terminal loss in striatal and nigrostriatal dopaminergic neurons.[77,79] Similarly, intensive treadmill exercise facilitates brain recovery in MPTP-treated mice, even when exercise commenced after neurotoxin-induced cell death was complete. These animals also demonstrated compensatory changes in the remaining dopaminergic neurons, such as altered dopamine handling (increased release and decreased uptake) and neurotransmission (increased dopamine D_2 receptor expression) in surviving dopaminergic neurons and their targets.[80] Exercise may also reverse the increased glutamatergic drive characteristic of the parkinsonian state at the level of striatal medium spiny neurons, by modulating the subunit composition of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (a glutamate receptor subtype), and by diminishing the amplitude of the spontaneous excitatory postsynaptic potential at glutamatergic corticostriatal terminals. Several potential exercise-induced mechanisms of neuroprotection and neurorestoration exist at the cellular level: elevation of transcription factors; activation of signal transduction pathways; and the induction of neurotrophic factors, such as brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor.[81,82]

Abbreviations: 6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

and perhaps to slow down progression in patients with overt PD. If exercise is proven to have disease-modifying effects, the ultimate goal will be to deliver strategies to postpone, or possibly prevent, the first disease manifestations in asymptomatic populations at risk of developing PD.

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Acknowledgments

The research work of M. Munneke and B. R. Bloem is supported by grants from ZonMw, The Netherlands Organization for Health Research and Development (75020012), The Michael J. Fox Foundation for Parkinson's Research, and the National Parkinson Foundation.

Author contributions

A. D. Speelman, B. P. van de Warrenburg, and G. Petzinger researched data for the article and wrote the manuscript. A. D. Speelman, B. P. van de Warrenburg, M. Munneke and B. R. Bloem made substantial contributions to discussions of the content. All authors contributed to review and/or editing of the manuscript before submission.