Parkinson Disease and Exercise

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ABSTRACT

Parkinson disease (PD) is a progressive, neurodegenerative movement disorder. PD was originally attributed to neuronal loss within the substantia nigra pars compacta, and a concomitant loss of dopamine. PD is now thought to be a multisystem disorder that involves not only the dopaminergic system, but other neurotransmitter systems whose role may become more prominent as the disease progresses (189). PD is characterized by four cardinal symptoms, resting tremor, rigidity, bradykinesia, and postural instability, all of which are motor. However, PD also may include any combination of a myriad of nonmotor symptoms (195). Both motor and nonmotor symptoms may impact the ability of those with PD to participate in exercise and/or impact the effects of that exercise on those with PD. This article provides a comprehensive overview of PD, its symptoms and progression, and current treatments for PD. Among these treatments, exercise is currently at the forefront. People with PD retain the ability to participate in many forms of exercise and generally respond to exercise interventions similarly to age-matched subjects without PD. As such, exercise is currently an area receiving substantial research attention as investigators seek interventions that may modify the progression of the disease, perhaps through neuroprotective mechanisms.


Introduction

Article overview

Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease. The economic cost of PD is estimated to exceed $23 billion annually in the United States alone (114). PD affects between 1% and 2% of individuals over 65 years of age and 3% and 5% of those 85 or older (65). The incidence of PD may range from 8.6 to 19.0 per 100,000 inhabitants based on a number of studies from the United States and Europe employing strict diagnostic criteria (249). However, the prevalence of PD as determined from community-based studies ranges between 100 and 200 per 100,000 individuals (4). Currently, approximately 6 million people are affected by PD worldwide (253).

Considerable evidence suggests physical activity or exercise provides numerous benefits for individuals with PD. These benefits include improvements in physical functioning and health-related quality of life and may also favorably influence disease progression. The latter has only been rigorously investigated in animal models of PD, but the neuroprotective and disease-modifying effects have prompted a surge of recent investigation in humans. Therefore, our objectives for this article are threefold: (i) provide an overview of PD, its symptoms and current treatment, (ii) describe how PD impacts physical functioning, and (iii) highlight the effects of physical activity or exercise on PD. The beneficial effects of exercise in PD on other domains (e.g., cognition, quality of life, etc.) have been comprehensively reviewed elsewhere (1, 44, 233).

Section 1: Overview of Parkinson Disease

Risk Factors for PD

Age appears to be the greatest risk factor for PD, but many other contributing factors have also been identified. Men are at greater risk than women, with a male to female ratio of 1.46 (241). It is unclear whether female hormones may be neuroprotective and/or if there are gender differences in the complex mix of genetic, acquired, and environmental factors that likely contribute to PD. Many specific genetic mutations have been identified including α-synuclein, Parkin, PINK1, DJ-1, and LRRK2 among others, for reviews see references (16, 72, 140). However, inherited forms of PD account for only 5-10% of cases and most of these are early onset forms (16). Mode of inheritance may be either autosomal dominant or...
recessive and the constellation and progression of symptoms differs with the different genes. A common mechanism of all of these genes is that they are all associated with mitochondria and they all interact with and influence the pathways for oxidative stress and free radical damage. Mutations may disrupt the function of mitochondrial complex I leading to reduced ATP synthesis and excess production of reactive oxygen species (11). Dopaminergic cells are particularly sensitive to oxidative stress and this may be one reason that cells of the SNpc die in PD [see references (37, 100, 219)]. Many of the identified nongenetic contributors to PD may also influence mitochondrial function and oxidative stress.

Exposure to pesticides has been associated with an increased risk of PD, as has farming, drinking well water, gardening, rural living, exposure to metals, and eating a diet high in animal fats (31). Exposure to environmental risk factors early in life, and even during gestation, may also reduce the number of dopaminergic cells and increase their susceptibility to cell death (10, 155). Additional factors associated with increased risk of PD include head injury and stress (22, 230). Only a few factors have been linked to a reduced risk of PD. These include cigarette smoking and coffee drinking, as well as use of nonsteroidal anti-inflammatories (31). A recent meta-analysis of emerging epidemiological evidence suggests that greater levels of moderate to vigorous physical activities are associated with a reduced risk of developing PD (35, 113, 145, 242, 263). For example, Thacker et al. reported the relative risk of developing PD among individuals who regularly exercised at moderate intensity compared to those who did no exercise was 0.6. (Moderate activity was defined as ≥ 16 MET-h/wk for men and ≥ 11.5 MET-h/wk for women and included activities like biking, swimming, jogging/running, tennis, and aerobics.) Light physical activity, which included walking and dancing, was not associated with a reduced risk of PD. At present, it is unclear whether exercise may protect against PD or if those with preclinical PD may be less active.

**Symptoms, Staging, and Progression**

The diagnosis of PD is made based upon clinical criteria, with a confirmation of this diagnosis possible only on autopsy. There are four cardinal features of PD: bradykinesia, rigidity, resting tremor, and postural instability. Bradykinesia refers to slowness of movement and is one of the most easily recognized symptoms of PD. Rigidity refers to an increased resistance to passive movement. The resting tremor of PD has a characteristic frequency of 4 to 6 Hz that normally disappears during active use of the affected body part, though individuals with PD may also demonstrate postural tremor. Postural instability is the most common cause of falls in those with PD and is often most pronounced in the backward direction (109). However, the latency to onset of falls in PD is typically several years and early onset of falls in the course of disease is reason to suspect an alternative diagnosis, such as progressive supranuclear palsy or multisystem atrophy (119). Other features of PD include a flexed posture and freezing, or motor blocks. The onset of motor symptoms in PD is typically unilateral, with the side of onset often remaining more affected throughout the course of the disease. PD is also associated with a number of nonmotor symptoms that are often overlooked but could influence the ability to participate in and/or benefit from exercise. These include autonomic disruptions such as orthostatic hypotension and sweating dysfunction, pain, sensory symptoms, cognitive changes, sleep disorders, fatigue, loss of motivation, anxiety, and depression (65).

The symptoms and signs of PD and their progression may be highly variable from one person to the next (73, 195, 259). This variability may be related to the topographical sequence of disease progression as well as to the extent of neuronal degeneration at these various sites. There are several methods used to characterize disease severity, or progression. These include classification on pathological findings (i.e., Braak staging) as well as signs and symptoms of the disease [i.e., Hoehn and Yahr and Unified Parkinson’s Disease Rating Scale (UPDRS)]. Braak staging is based upon characterization of Lewy bodies, proteinaceous intraneuronal inclusions, and their spread as the disease progresses (23). Six stages have been proposed, as has a predictable topographical sequence of Lewy body deposition. According to this scheme, signs and symptoms of PD do not appear until stage 3 to 4 when the substantia nigra pars compacta is first affected. Other scales rate the severity of PD based upon signs and symptoms rather than pathophysiology. One such rating method is Hoehn and Yahr (106) staging. Stage 1 describes unilateral disease, stage 2 bilateral disease, stage 3 bilateral disease with postural instability, stage 4 loss of physical independence, and stage 5 a wheelchair-bound or bedridden condition. This staging method is often used to define inclusion/exclusion criteria for studies examining individuals with PD (84). Another scale that rates disease severity based upon signs and symptomatology is the UPDRS (83). The UPDRS includes four separate scales for nonmotor (scale I) and motor (scale II) experiences of daily living, motor examination (scale III), and motor complications (scale IV). These individual scales can be summed to obtain a total score, or used individually to obtain subscores. Subscores on the UPDRS-III motor examination are often reported as an outcome measure in studies examining the effects of exercise in those with PD. It should be noted that it is now generally accepted that prior to the motor phase of classical PD there exists a prodromal period comprised mostly of nonmotor features (e.g., olfactory, autonomic dysfunction). This is a developing area that has recently been reviewed elsewhere (99).

**Treatment of Parkinson Disease**

While there is no cure for PD, many of the symptoms of PD are responsive to dopamine replacement treatment. Levodopa, a dopamine precursor that can cross the blood-brain barrier and is then metabolized into dopamine, provides the most effective
symptom relief. However, long-term treatment with levodopa is associated with motor complications such as dyskinesias and motor fluctuations. Dyskinesias are choreatic involuntary movements induced by the medication. Motor fluctuations refers to wearing off of the effect of medication prior to the next dose (196, 224). These complications are common, affecting more than 50% of those treated with levodopa for more than 5 years (182). Additional measures can be taken to address PD symptoms and treat motor fluctuations, including the use of dopamine agonists, monoamine oxidase-B inhibitor, and catechol-O-methyltransferase inhibitors (141).

Surgical treatment of PD has changed dramatically in the past decades with the advent of deep brain stimulation (DBS). Stimulating electrodes can be permanently implanted into target nuclei to deliver typically high-frequency electrical pulses. The most common target for DBS was initially the globus pallidus internal segment (GPI), but has shifted to the subthalamic nucleus (STN). STN stimulation appears to provide a larger improvement in off-medication symptoms (50). STN DBS can also allow recipients to reduce their dosage of levodopa, thereby reducing motor complications associated with the medication (188). However, there are some features of PD that do not respond well to either medication or DBS, such as “on period freezing,” postural instability, and dementia. These dopa-resistant and STN DBS-resistant symptoms are thought to be related to degeneration in nondopaminergic systems. However, early evidence from the newest target for DBS, the pedunculopontine nucleus (PPN), suggests that PPN stimulation may positively influence freezing and postural instability (87, 148). There are no studies to date comparing the effects of exercise in people with PD with versus without DBS. However, there is currently no reason to suspect that individuals with DBS would respond differently to exercise than individuals without DBS.

While new drugs and new surgical approaches to treat PD are continually being developed and refined, no pharmacologic or surgical approach has been shown to cure PD or definitively modify disease progression. As such, it is clear that additional avenues need to be explored to address the disease. One approach that has long been overlooked, but has gained prominence in the past decade, is the role of exercise in disease management. The virtual explosion in the area of exercise research in PD may be attributed, at least in part, to emergence of evidence of the possible neuroprotective effects of exercise in animal models of PD. In 2001, Tillerson et al. (245) demonstrated a decrease in the extent of dopamine terminal degeneration in a toxin-induced rat model of Parkinsonism as a result of forced use of the affected limb. The following year, they reported that forced nonuse of the affected limb exacerbated neuronal degeneration (244). The suggestion that physical activity may be protective and physical inactivity may potentiate neuronal loss was groundbreaking. Since this time, additional studies of exercise effects in animal models of Parkinsonism have yielded mixed results. Some demonstrate neuroprotective effects from exercise (64,112,149,265), while others demonstrate enhancement of physical function with no evidence of neuroprotection (2, 176). There are, to date, no definitive studies that examine whether or not exercise in humans with PD has a neuroprotective effect, though several trials are underway that will attempt to determine whether exercise modifies disease progression. We present a hypothetical model of how exercise may attenuate or delay the progression of Parkinsonian symptoms (Fig. 1). Irrespective of a neuroprotective effect, it should be noted that studies implementing exercise as a therapy have not reported any serious adverse effects or provided any evidence of acceleration or exacerbation of signs and symptoms of PD. The remainder of this article details what we know at present about the effects of PD on individuals’ physical activity and ability to participate in exercise as well as the responses of people with PD to participation in various forms of exercise.

Section 2: Effects of Parkinson Disease on Physical Activity

Gerontology research has clearly identified an age-associated steady decline in neuromuscular function beginning in the sixth decade that presents with impairments in mobility and is associated with a variety of adverse health events (252). The sixth decade period of life also denotes the average onset of PD. Researchers have characterized PD as accelerated aging (82, 228) because the initial symptoms are similar to normal aging yet the magnitude and progression of these impairments are more rapid. The results of these progressive symptoms, both motor and nonmotor, are discussed below to highlight the influence of PD on physical activity and exercise performance. Throughout the rest of this article we will use the term “physical activity” to mean nonspecific physical exertion whereas “exercise” or “exercise performance” refers to a specific task with defined parameters.
Force Production

Muscle weakness in PD has been recognized as a primary symptom (124), a secondary cause of bradykinesia (14), and a contributing factor in postural instability (168). Considering the effects of normal aging alone, average maximal isometric strength is approximately 20% to 40% lower in those in their seventh and eighth decades of life, and 50% or more in those who are very old as compared to younger adults (252). These differences are magnified in individuals with PD, as several studies have reported those with PD to be weaker than those without PD of similar age, see Falvo et al. (2008) for review (67). This suggests PD contributes uniquely to the decline in force production. It should be noted that terms such as “strength” or “muscle weakness” are often used in the literature with ambiguity. Strength may be considered in terms of magnitude, as with maximal voluntary contraction (MVC), or may be characterized in terms of velocity by examining rate of force development (RFD). Therefore, if an individual with PD is found to have a lower MVC and/or slower RFD—this would be evidence of muscle weakness. In keeping with the bradykinetic movement characteristic of PD, decreases in RFD (41, 123, 178, 179) and prolonged contraction times (41, 123, 236, 257) are commonly observed. Most studies also find MVC to be reduced in those with PD compared to controls (115, 133, 168, 178, 179, 185, 186), and in some cases a decline in MVC is associated with a similar decrease in RFD (41). Decrements in both the magnitude and rate of force production underscore the importance of targeting interventions to attenuate this force loss (67), which are highlighted in Section 3.

The mechanisms underlying impaired force production in PD are not fully understood, but have been suggested to be a function of the inability to fully activate the motor neuron pool of the active muscle (81). Several lines of evidence support this view, including electrophysiological data that demonstrate alternating bursts and tonic background activity in the electromyographic (EMG) signal (204), thought to compensate for decreased muscle activation (24, 25, 82, 205, 206). Underactivation of cortical motor centers, recorded via electroencephalography (EEG), has also been observed in those with PD compared to controls (40), further suggesting a centrally mediated mechanism governing reduced force production. Consistent with these data, and consistent with a central origin of weakness, is the improvement in strength that occurs following administration of anti-Parkinson medication (41, 168, 184) and with DBS of the STN (250).

Falls, Fractures, and Osteoporosis

Fall risk increases with age in the general population and this rate is further elevated in PD (69). Estimates suggest that 70% of those with PD fall annually, and 13% fall multiple times weekly (134, 260). As a result, falls are the most common cause of emergency hospital admissions in those with PD (261). Recent studies (51, 207) have attempted to identify falling risk factors specific to PD which are summarized in Table 1. Interestingly, there are several potentially modifiable factors that may be targeted via exercise interventions, lower-limb strength being an example. Reduced muscle strength of the lower limbs is already recognized as one of the most important risk factors for falling in elderly without PD and may be used to identify those prone to falls (194). Similarly, researchers demonstrated that decreased proximal strength of the legs could be used to distinguish between fallers and non-fallers with PD (207). As evident from Table 1, strength is only one of several factors that should be addressed to reduce fall risk. Unfortunately, very few exercise interventions designed to minimize these risk factors have been rigorously evaluated despite the available recommendations [c.f. Table 12 in reference (207)].

Fracture risk is also much higher in individuals with PD than those without (121, 214), which is not altogether surprising given the higher incidence of falls. Two retrospective cohort studies found overall fracture rate to be 7.5% to 15% higher in those with PD as compared to their age- and gender-matched controls (78, 121), with femoral neck fracture about five times more common in PD (121). Recently, in a prospective cohort design, women with PD had a 2.6-fold higher age-adjusted risk for hip fracture than women without PD (223). Irrespective of study design (i.e., case control, prospective) the literature clearly supports greater incidence of fracture which may be related to fall frequency and/or to osteoporosis.

Attention has been drawn to the association between PD and low bone mineral density (BMD) in multiple case-control studies (202, 215, 216). As a recent example, Bezza et al. (15) compared 52 individuals with and without PD using dual energy X-ray absorptiometry and observed significantly lower BMD at the hips and spine of those with PD. They found 31.3% and 50% of women and 11.1% and 55% of men with PD to have osteoporosis and osteopenia, respectively. BMD was significantly correlated with age, disease stage, body mass index, sunlight exposure, and calcium intake (15). Previous studies corroborate these findings, as low BMD has been significantly correlated with disease severity, body mass index, and disease duration (52, 125, 264).

Table 1 Falling Risk Factors for PD

| • Disease duration, severity |
| • Extent of disability |
| • Drug-induced dyskinesia |
| • Freezing of gait |
| • Postural instability |
| • Abnormal proprioceptive motor integration |
| • Decreased lower-limb strength/endurance |
| • Orthostasis |
| • Depression |
| • Fear of falling |

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Work from Sato and associates has demonstrated that low BMD may be exacerbated in individuals with PD that have 25-hydroxyvitamin D deficiency as a result of a lack of sunlight exposure (213, 216, 217). This scenario likely induces compensatory hyperparathyroidism which, along with immobilization, increases bone resorption which may contribute to the incidence of hip fractures (213, 217). Invernizzi et al. recently reviewed the topic of osteoporosis in PD and identified reduced mobility, endocrine, nutritional, and iatrogenic factors to play an important role in reduced bone mass (116). In addition, they identified that the most severe cases were found in women as well as those with greater disease duration and severity. Although additional research is necessary in these areas, Genever et al. (78) has called to attention that despite mounting data, individuals with PD still are not routinely prescribed bone-protecting medication or referred for densitometry. Although osteoporosis screening has been recommended for both women (Schneider et al., 2008) and men (69) with PD, it is not clear if this has been adopted as the current standard of care. This, along with the paucity of intervention studies, makes BMD an essential line of research.

Fatigue

Fatigue affects as many as 30% to 56% of patients with PD (5,76,127,147,225), yet it is poorly understood and frequently overlooked (75). A possible reason for this oversight, identified by Grace et al. (86), is that the UPDRS does not include any questions specific to fatigue. However, fatigue is a major factor influencing quality of life in individuals with PD (200). The literature on fatigue in PD is growing and several quality reviews are available (34, 75, 146, 167, 267).

In a study from the ELLDOPA clinical trial (66), investigators separated levodopa-naive individuals with PD into fatigued and nonfatigued groups using a cutoff score of 4 on the Fatigue Severity Scale (1-7 range with 7 being the most fatigued) (137), and found fatigued subjects to be significantly more neurologically impaired, as determined by subsets of the UPDRS (220). However, groups were not different on striatal dopamine transporter density, suggesting the pathogenesis of fatigue may be only partly the result of nigrostriatal dopaminergic deficiency (220). This was supported by a study by Hagell and Brundin (94) in which, after accounting for anxiety, depressive symptoms, and the lack of motivation, Parkinsonism explained only 3.6% of unique variance in fatigue (94). Although levodopa was shown to reduce the progression of fatigue in the ELLDOPA trial (220), associations between fatigue and anti-Parkinson medications were not found by Hagell & Brundin (94). It is also unclear whether the severity of PD is related to fatigue as correlations have been reported in some (5, 94), but not all studies (76). These discrepancies may also reflect the sensitivity of fatigue measures in individuals with PD.

Garber and Friedman (77) studied the effects of fatigue on exercise performance in individuals with mild to moderate PD. This study found those with greater fatigue had lower levels of physical activity and performed poorer on the timed up-and-go and VO2 max test than those patients without fatigue. In regards to lower physical activity levels, the authors pointed out that it was indeterminable whether fatigue contributed to or was the result of a sedentary lifestyle. Excluding this study, limited data are available describing the effects of fatigue on measures of exercise performance.

Locomotion and Aerobic Capacity

Perhaps even before diagnosis, those with PD may begin to notice reductions in walking speed and step length (162). As PD progresses, so too do gait disturbances including increased time spent in stance and double support phases (30), quicker cadence with shuffling steps (i.e., festination) (98), and a reduced amplitude of arm movement (163,165). These features, may combine with the characteristic flexed posture, decreased range of motion of the lower extremities (68, 160, 163) and diminished kinetic output to create a precarious gait profile. Regarding the latter, ground reaction forces recorded during heel-strike and push-off as well as joint power production of the lower limbs are reduced during gait in those with PD (68, 132, 156, 164, 165, 171). This kinetic profile supports the aforementioned reports of greater muscle weakness in individuals with PD, but may also reflect other factors such as limited range of motion about the joint and impaired interlimb coordination.

Although studies examining straight-line walking are informative, normal daily living involves navigation and requires turns. Turning for those with PD may be challenging, and difficulties have been reported in over 50% of patients (19, 170, 234). For healthy adults, turns are executed with a cranio-caudal sequence (183) whereas in PD turning is performed en bloc, or with little movement between body segments (42,163). Despite differences in segmental control, muscle activity patterns of the lower limbs are similar (107), highlighting a difficulty in scaling movement amplitude (160). This type of en bloc turning may contribute to the association seen between turning difficulties and fall risk (19, 170, 234). Related to this is the phenomenon of akinetic blocks, or freezing of gait (FOG), that occur frequently when turns are attempted in those with akinetic history (80). FOG is more common in individuals with advanced stages of PD (150) and likely further increases the risk for falling (21). Hallett (95) suggests that FOG results from a myriad of problems specific to PD, both intrinsic and extrinsic to the disease. As FOG is difficult to replicate in a laboratory or clinical setting (172), much is to be learned regarding its underlying mechanisms and treatment.

The combined features of Parkinsonian gait (i.e., reduced speed, step length, range of motion, force, and FOG) can be considered concurrently during performance of the
Postural Instability

One of the hallmark symptoms of PD, postural instability, is a main contributor to increased fall frequency and fall-related injuries (6, 7). As a result, many people with PD have a heightened fear of falling which often restricts their physical activity resulting in a deteriorating quality of life and health status (166). Current understanding of the pathophysiology of postural instability is insufficient, which is likely the result of its complexity as well as the insensitivity of balance measures. Maladaptations in a variety of postural systems are thought to be at work including abnormal postural reactions and responses, poorly directed compensatory arm movements, as well as ineffective sensory integration (17, 109, 169). To this end, it has proven difficult to characterize postural stability by employing only a limited clinical battery. Several authors (54, 117) recommend assessing different types of postural stress through multiple balance tests to capture the full clinical picture of postural stability.

To complicate treatment, postural instability may even be resistant to dopamine replacement therapy (18, 110). This is distinct from the other cardinal symptoms of PD that respond favorably, and underscores our developing understanding that the clinical manifestation of PD does not exclusively reflect a hypodopaminergic syndrome (88). This is supported through neuroimaging (i.e., fluoroDopa PET) whereby nigral cell loss exhibits a very strong correlation with bradykinesia, but is much weaker with postural instability (254). This has led researchers to study other nuclei and neurotransmitters that may also be susceptible to PD. The adrenergic hypothesis has also been put forth by Grimbergen and colleagues (88), which suggests postural disturbances in PD may be the result of cell loss in the locus coeruleus. The locus coeruleus relies mainly on norepinephrine to perform a variety of functions that may be associated with balance, namely autonomic responses, cognition, and motor control (88). To support this hypothesis, postmortem studies have demonstrated significant cell loss in the caudal region of the locus coeruleus in those with PD (32, 108), a region that is otherwise unaffected by normal aging (33, 120). Recent evidence also supports the role of the PPN on postural stability (126, 193, 235), which is suggested to influence gait and locomotion (180). The PPN receives inhibitory input from GPi/SNr and projects back to the basal ganglia, cerebral cortex, and spinal cord (235), so it is well-situated to influence postural stability. It has been posited that a reduction in inhibitory output from GPi/SNr to PPN may improve postural stability (180). Karimi and colleagues (126) support this hypothesis by demonstrating a negative correlation between regional cerebral blood flow and improved postural stability. Moreover, it has been shown that DBS of PPN and STN results in greater postural improvement than DBS of STN alone (235). As research in this area is relatively recent, well-controlled trials are needed to support hypotheses regarding the role of nondopaminergic systems in the progression of PD.

Section 3: Effects of Physical Activity on Parkinson Disease

Despite surgical and pharmacological advances, progressive motor impairments necessitate additional rehabilitation therapies to maximize the function and independence of those with PD (49). Such therapies have included a variety of physical therapy techniques including sensory cueing and behavioral therapies that have been the subject of several systematic reviews (48, 49, 128) and meta-analysis (47). Consistent amongst these reviews is the absence of “best practice” or “standard” physical therapy techniques that is due, in part, to the lack of well-controlled studies. Much less studied are the effects of structured exercise interventions in individuals with PD which was highlighted by a recent meta-analysis identifying only 14 randomized controlled trials as of 2006 that assessed the effects of exercise or physical activity on physical performance, falls, or quality of life in PD (85). Despite the paucity of data, the efficacy of physical therapy (47) and exercise (43, 85) appears to be beneficial in regards to performance of activities of daily living and functional mobility.

In recent years, research has accelerated in various areas of exercise. This increase is not without merit as physical exercise has demonstrated a reduction in mortality rate in PD (138) as well as a slight protective effect on the risk of PD (35, 212). Perhaps more intriguing are several lines of evidence from animal models that demonstrate the brain’s ability to repair itself through exercise (231). Experimentally, exercise may be effective by way of stimulating the synthesis of dopamine via increased serum calcium levels (239) or upregulating trophic factor expression (231). Irrespective of mechanism, the promotion of neuronal growth and/or reduced vulnerability of dopamine cells are examples of activity-dependent neuroplasticity. Although exercise-induced neuroplasticity evidence is available in PD animal models (266), only one study has examined both brain and behavior in humans (71). As research and technology progresses,
beyond the scope of this article [please see reference (162)],

...six core areas for physical therapy; transfers, posture, reach-

...additional general guidelines have been proposed by Keus and colleagues which focus on end-stage disease (162). Additional general guidelines have been proposed by Keus and colleagues which focus on end-stage disease (162).

...which to foster the greatest adaptations and results through rehabilitation. The ensuing paragraphs will discuss the effects of specific rehabilitative approaches in greater detail. We also highlight (Table 2) some innovative approaches in the field of exercise research in PD that warrant additional attention.

### Table 2  Novel Exercise Modalities for Individuals with PD

<table>
<thead>
<tr>
<th>Modality</th>
<th>Length of training</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tandem cycling (203)</td>
<td>8 weeks</td>
<td>• 35% improvement in UPDRS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cycling training improved upper extremity performance</td>
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<tr>
<td>Tango dancing (60)</td>
<td>12 month</td>
<td>• ~30% improvement in UPDRS</td>
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<tr>
<td></td>
<td></td>
<td>• Improved gait and balance</td>
</tr>
<tr>
<td>Eccentric recumbent stepping</td>
<td>12 weeks</td>
<td>• 6% increase in muscle volume</td>
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<td></td>
<td></td>
<td>• 24% increase in muscle torque</td>
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<tr>
<td></td>
<td></td>
<td>• 21% improvement in 6-min walk</td>
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...there is hope we may better understand the mechanisms by which to foster the greatest adaptations and results through rehabilitation. The ensuing paragraphs will discuss the effects of specific rehabilitative approaches in greater detail. We also highlight (Table 2) some innovative approaches in the field of exercise research in PD that warrant additional attention.

### Physical Therapy

The goals of physical therapy are broad and often target mobility impairments, posture, and balance through a variety of modalities. The number of studies of general physical therapy interventions is quite high, as the bulk of the literature on exercise focuses on this area rather than on specific forms of exercise such as strength training or aerobic exercise. Unfortunately, however, there is nonuniformity regarding physical therapy treatment approaches and therefore clear recommendations for PD are difficult. However, recent efforts by some investigators have addressed these concerns (129, 130, 175). From a theoretical perspective, physical therapists have approached PD rehabilitation in a manner that attempts to circumvent disrupted basal ganglia circuitry (e.g., cueing) to execute normal movements (161). Morris has suggested that therapists need not only consider external cues for optimizing movement, but should pay attention to medication as well as task-specific training for the individual (161). Factors unrelated to PD also largely influence the rehabilitation program design including the effects of aging, secondary pathologies, and cognitive impairments. To this end, Morris has recently outlined a robust long-term programming model for physical therapists in regards to locomotor training (162). This model encompasses individuals at various stages of disease severity, including those who are de novo, that is, those who have not yet begun dopamine replacement therapy, through those with end-stage disease (162). Additional general guidelines have also been proposed by Keus and colleagues which focus on six core areas for physical therapy; transfers, posture, reaching and grasping, balance, gait, and physical capacity (128). Description of these practical management strategies of PD is beyond the scope of this article [please see reference (162)], but these reviews do highlight the varied physical therapy approaches taken for PD rehabilitation. From this, it is apparent that no single mode or group(s) of exercises clearly defines “physical therapy” which likely accounts for the absence of a standard or accepted practice.

As of 2001, Cochrane reviews concluded that the evidence was insufficient to support or refute the efficacy of physical therapy in PD and no single therapy seemed to garner greater results than the others (48, 49). A more recent characterization of these physical therapy approaches has been conducted by Keus and colleagues (130) in which they provided a comprehensive review of the current status of evidenced-based physical therapy for PD (130). The authors identified 38 randomized controlled trials and controlled clinical trials as of January 2008, with approximately 48% of these trials conducted from 2005 to 2008. Despite some very promising research providing evidence for specific interventions, Keus and colleagues reiterated the need for more well-developed trials, with follow-up measures, that abide to the CONSORT statement of trial design (159).

### Cueing

One specific physical therapy strategy that is well supported is the efficacy of cueing training. The provision of external cues, such as stripes across a walkway, has been shown to improve motor performance (e.g., increase gait speed and reduce akinetic blocks) (8, 164). Given that dopaminergic neurons govern well-learned and automatic movements such as walking (208), when they are lost as occurs in PD, these movements become more difficult. Therefore, an individual’s internal cueing mechanisms become dysfunctional in PD. Bypassing the diseased basal ganglia through external cues (e.g., auditory, visual, and cutaneous) to gain access to the supplementary motor area via the thalamus (174) or premotor cortex via the cerebellum (38), may successfully circumvent impaired motor pathways.

The results of Nieuwboer et al.’s RESCUE trial (173) provide strong evidence for the utility of cueing. Their 3-week, home-based cueing program was designed to improve gait and quality of life in those with PD. This was the first large randomized controlled trial to demonstrate a 3-week program of rhythmical cueing had a significant positive impact on posture and gait (e.g., gait speed, step length, freezing, and timed balance). In addition, Nieuwboer and colleagues also provide evidence demonstrating that noted improvements were considerably diminished at the 6-week follow-up. The authors suggest the latter underscores the need for permanent cueing devices and follow-up treatment (173).

### Balance training

Recently, Dibble et al. (53) systematically reviewed the impact of exercise intervention studies on balance outcomes for individuals with PD utilizing the WHO’s International Classification of Functioning, Disability, and Health (ICF) model.
Using the ICF model and the authors’ search strategy, 21 studies were identified. Regarding the effectiveness of physical activity and exercise, authors found moderate evidence supporting improvements in postural instability and balance task performance, limited evidence for enhanced quality of life, and weak support for exercise to affect falls and near-fall events. Interventions considered in this review included a variety of modalities ranging from martial arts and music therapy to progressive resistance training.

It is infrequent that balance is addressed exclusively in a training program; rather, it is included under the umbrella of physical therapy exercises. However, Qutubuddin and colleagues (199) randomly assigned individuals with PD to either a computerized dynamic posturography or standard physical therapy to compare two methods of balance training. Both groups demonstrated improvements on selected outcomes, but no differences were observed between groups. Although it is attractive to suggest that less sophisticated therapy is equally effective, this study suffered from high attrition rate, high variability in outcome measures, and a limited description of treatment protocols.

To our knowledge, only one other study has specifically focused on balance training alone for individuals with PD. In this study (62), authors randomized 27 individuals with PD to either a whole body vibration training program or conventional physical therapy (e.g., tilt board exercises) condition. Training was performed twice daily for 15 min per session, 5 days per week, for 3 weeks. Clinical assessments of mobility and postural stability demonstrated improved performance in both groups that remained stable for 4 weeks after the cessation of either treatment. No differences were observed between vibration and standard therapy.

**Resistance Exercise**

A clear rationale for resistance training in PD has been suggested previously (45,67), yet data remain limited as very few well-controlled trials have been performed. Of these, less than ten studies are available that adequately describe the exercise training program (i.e., mode, volume, temporal expression of force, etc.) as well as utilize outcome measures that assess physical functioning (56,57,96,105,218,221,246). These investigations studied patients considered to be mild-moderate in their disease progression, but their approaches were distinct. Overall, data do support that resistance exercise significantly improves force production (55,57,96,105,218,221), muscular endurance (96,218), and muscle size (56) in individuals with PD. Perhaps more importantly, a program of resistance training has also been shown to be efficacious in improving measures of gait performance (56,57,218), balance (105), mobility (56,96), and perceived quality of life (57).

Although there are significant data that report individuals with PD exhibit impaired force production and greater fatigability compared to their healthy age- and gender counterparts (see Section 2), only one resistance training study has included control subjects without PD (218). Investigators had participants perform lower body exercises 2 d-wk\(^{-1}\) for eight weeks at a moderate intensity. Exercise volume increased similarly in both groups over 8 weeks, and no between-group differences were noted at posttesting. This led the authors to suggest that those with PD can achieve comparable exercise improvements to those of neurologically healthy adults. A take-home message from this study is that individuals with PD are equally capable of participating in and deriving similar benefits to a resistance training program akin to age-matched neurologically normal adults. Dibble and colleagues (56,57) subsequently capitalized on this potential and safely and effectively administered a novel mode of high-intensity resistance training—eccentric ergometer—to individuals with PD. Authors split subjects into two exercise groups, the only difference being performance of either eccentric or traditional lower-body strength training. Muscle hypertrophy (+6%), torque (+24%), and 6-min walk time (+18%) were significantly greater with eccentric compared to traditional training (56). More recently (57), they repeated the same design with the purposes of addressing bradykinesia. The authors quantified bradykinesia via the timed up-and-go task and the time to walk 10 m. Although all subjects experienced considerable improvement in strength, mobility, and quality of life, those performing eccentric exercise experienced significantly greater improvement in the timed up-and-go (e.g., +17% vs. +2%) and 10 m walk (e.g., +12% vs. +2%) (57). Both of these investigations (56,57) clearly highlight high-intensity resistance training as a feasible and important component of exercise interventions.

In a recent systematic review on progressive resistance exercise in PD, David et al. (2012) summarized important limitations of the currently available research (45). These include the lack of studies evaluating patients both on and off antiparkinson medication, lack of long-term follow-up, few investigators including the UPDRS as an outcome measure, and the varied resistance training designs and approaches. These characteristics make it a challenge to define the optimal resistance training prescription for individuals with PD. However, more recent data (3,55-57) provide some evidence that higher intensities may be particularly beneficial.

**Cardiovascular Exercise**

Mounting evidence from multiple disciplines widely supports the inclusion of aerobic exercise for improving cognition and brain function across the lifespan [For review, reference (104)]. Aerobic exercise may result in improvements in behavior and cognitive function in those with dementia and related cognitive impairments as determined via meta-analysis (103). Older adults assigned to a 6 month aerobic exercise intervention even demonstrated an increased volume in both gray and white matter. These gains were primarily in prefrontal and temporal cortices (39), regions prone to
age-related deterioration. Despite these obvious advantages of aerobic exercise, well-designed studies are lacking in those with PD and only recently have such interventions been pursued. This recent interest may be due, in part, to promising data derived from animal models of PD.

Studies from several laboratories have demonstrated that cardiovascular or aerobic exercise can have a neuroprotective effect in both the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned mouse and 6-hydroxydopamine lesioned rat (70, 192, 243, 266) models. Compared to sedentary lesioned rodents, those rodents engaged in treadmill training twice daily for 10 days, beginning one day postlesion, demonstrated complete behavioral recovery, significant sparing of striatal dopamine, and an increase in dopamine transporter levels (243). In this study, immediate exposure to exercise (e.g., 12 h postlesion) was found to be associated with an attenuation of dopamine loss. Fisher et al. (70) and Petzinger et al. (192) delayed the introduction of exercise until 4 to 5 days after MPTP lesioning, when cell death is thought to be complete. These studies also exercised lesioned MPTP mice at a higher intensity (i.e., 2 d·wk⁻¹, 30 min per session), greater frequency (i.e., 5 d·wk⁻¹) and longer duration (i.e., 28-30 days) than Tillerson et al. (243). Intense treadmill exercise led to improvements in velocity, endurance, and balance. Collectively, neuroprotective benefits of treadmill exercise are well observed and may act through modulation of genes and proteins specific to basal ganglia function (70).

Herman et al. (102) recently reviewed the effects of treadmill training on individuals with PD and found nine published long-term (3.5-12 weeks) intervention studies (28, 71, 101, 139, 157, 158, 197, 229, 247). Although authors point out limitations in the quality and sample size of investigations, consistent improvements were noted for gait, mobility, and quality of life. It has been speculated that there are some unique aspects of treadmill training that may help foster these improvements. First, the inherent design of a treadmill forces individuals to maintain a predetermined rather than voluntary walking speed. Given the neurophysiological (58) and neuroimaging (118, 210) data demonstrating reduced neural activity in cortical motor areas of those with PD, it has been suggested that this may limit their ability to exercise at a high frequency and that exercise rate may need to be controlled externally (203). Walking on a moving treadmill belt activates proprioceptive and vestibular receptors to provide repetitive sensory feedback to the central nervous system (102, 153) as well as activating central pattern generating circuits (251). These paced, rhythmic motor commands activating muscles of the limbs required for treadmill walking may reinforce synaptic connections through a form of motor learning (102). This has been realized in response to treadmill training as individuals adopt a more uniform gait cycle, leading some investigators to view the treadmill as a type of external pacemaker (74). Additionally, further up the neuraxis, Fisher et al. (71) have demonstrated enhanced corticomotor excitability following 8 weeks of treadmill training, a finding that complements the aforementioned animal data in regards to the neuroplastic changes that may result secondary to exercise.

Consistent amongst these human studies is that exercise has been voluntary rather than forced. A forced-exercise paradigm (i.e., exercise at a rate that exceeds preferred voluntary rate) has demonstrated neuroprotective properties and improved motor function in animal models of PD (190, 191, 192, 240, 269), but only recently has been translated into a human model. Alberts and colleagues implemented forced exercise via tandem bicycling in which individuals with PD were assigned to 8 weeks of either tandem (forced) or stationary (voluntary) cycling (203). Although aerobic intensity was consistent between groups (i.e., 60%–80% of heart rate reserve), those assigned to the forced exercise group produced less power per exercise session (47 watts) than those in the voluntary exercise group (67 watts). Still, only those performing forced exercise exhibited a 35% improvement in UPDRS motor scores whereas no improvement was observed in the voluntary exercise group. Similarly, forced exercise of the lower extremities resulted in improvement in upper extremity function (i.e., bimanual dexterity), suggestive of a transfer of training effect, but were not evident in the voluntary exercise group. Authors are currently conducting a randomized controlled trial to follow-up this initial study (3).

### Complementary Approaches to Exercise in PD

In addition to traditional exercise approaches, there are many complementary avenues of exercise in which individuals with PD may participate. Evidence regarding these complementary approaches is even more limited than evidence regarding traditional exercise approaches, but as with traditional exercise, this is an area that is of increasing interest and much current research.

#### Dance

Dance may be an excellent form of exercise for those with PD because it can address each of the key areas that have been identified as important for a PD exercise program (128). These key areas include: (i) the use of external cues, (ii) teaching and practice of movement strategies, and (iii) dynamic balance exercises. Dance incorporates practice of many functional movements that people with PD may struggle with, including backward walking and turning. Another important feature of dance may be that it is, by nature, an activity that requires multitasking. People with PD are known to have particular difficulty walking while performing a secondary task (20, 177), but practice in multitasking situations can improve performance (227, 262). In addition, dance can result in improved cardiovascular function, a testament to the fact that, if done with sufficient intensity, dance is an excellent form of aerobic exercise. Waltzing can provide cardiovascular benefits
equal to those of treadmill training (13). The cardiovascular effects of dancing tango have also been probed, and tango elevates heart rate to approximately 70% of maximum which is in the appropriate range for aerobic training (187).

There are limited numbers of studies to date that examine the benefits of dance for individuals with PD. Only one study reported improvements in movement initiation with dance (255), and two have reported improvements in quality of life (91, 256). Several studies have now reported significant improvements in balance, 6-min-walk distance, and gait velocity in groups with PD who participated in Argentine tango or waltz/foxtrot classes (90, 92, 93). These changes were both statistically and functionally meaningful, as they exceed defined thresholds for meaningful changes in each of these measures (61). Most recently, a long-term tango program of 12 months duration was shown to significantly reduce motor symptom severity, as assessed using the UPDRS with participants off medication (60). This work suggests that regular participation in dance exercise may modify the progression of disability in PD. There are no studies to date investigating the neural mechanisms by which dance may have beneficial effects in individuals with PD. Practice of dance may facilitate activation of areas that normally show reduced activation in PD. Brown et al. (26) showed that performance of tango movements to a metered and predicoted beat was associated with increased activation of the putamen in healthy controls. Sacco et al. (211) showed that healthy controls who learned to dance tango showed a shift in cortical activation, with increased activity in the premotor and supplementary motor areas during imagined walking following a series of tango lessons. They propose that tango, which has walking as its basic step, may serve as a means of focusing conscious attention on walking. Devoting conscious attention to walking is known to improve gait in individuals with PD when they focus on walking quickly with large steps (9, 164). With focused attention on walking during tango dancing, movements may become more automatic resulting in enhanced performance that no longer requires conscious attention. For a review of the literature regarding dance and PD please see Earhart (61).

Diet and Nutritional Supplements

Another alternative approach to PD that may influence or be related to exercise is the modification of diet and use of nutritional supplements. Evidence from toxin-induced models of PD in animals suggests a potential neuroprotective effect of caloric restriction (59, 152). In addition, high calorie intake has been linked to a greater risk for developing PD (122, 144). Much research remains to be done in this area. Additional research is also needed to determine the effects of dietary supplements on PD. More than 50% of individuals with PD use some sort of dietary supplement and nearly half of these individuals do so without the knowledge of their treating physician (258). The most commonly used supplements are multivitamins and vitamin E (201), despite strong evidence to suggest that vitamin E provides no benefit (181). Vitamin E is one of several antioxidants that have been investigated for their neuroprotective potential, given the possible relationship between mitochondrial impairment and neurodegeneration. Others include selenium and coenzyme Q<sub>10</sub>. Selenium has been shown to protect nigrostriatal neurons from degeneration in animal models, but human studies have yet to be developed due to methodological difficulties in measuring selenium levels in people (131, 268). Studies of coenzyme Q<sub>10</sub> in animal models have also shown promise of neuroprotection (12, 135, 154, 232). However, results from human studies have been mixed, with some showing improvements in UPDRS scores with high doses and others showing no effect (226, 237). For a more thorough review of these topics see Toulouse and Sullivan (248).
Conclusion

Individuals with PD present with a range of motor and nonmotor symptoms. In addition, they also face the effects of normal aging as well as any secondary pathologies and comorbidities. Taken together, these challenges often confer a reduced quality of life and in some cases, a “self-chosen home arrest” (79). Treatment has been approached primarily through medication and neurosurgical treatment, but these come with their associated limitations, namely a finite time course of efficacy, surgical risks, and incomplete control of treatment-resistant symptoms. To this end, alternative methods of attenuating disease progression and improving movement control without adverse effects, such as physical therapy and exercise, have been investigated. The literature clearly supports the efficacious use of such approaches as adjuncts to traditional treatment, specifically related to quality of life, locomotion, balance, and strength (85). It has yet to be determined whether exercise has a neuroprotective and/or disease modifying effect in individuals with PD (Fig. 1). Future research is essential in resolving the mechanisms underlying exercise-related improvements and for determining the optimal exercise mode and associated training variables (i.e., intensity, frequency, and duration).

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