HHS Public Access

Author manuscript

Clin Ther. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Clin Ther. 2018 January ; 40(1): 8–15. doi:10.1016/j.clinthera.2017.11.004.

Effects of Exercise on Non-Motor Symptoms in Parkinson's Disease

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Abstract

Parkinson's disease patients experience disabling non-motor symptoms including autonomic dysfunction, cognitive decline, and sleep disorders. Pharmacologic treatments for these symptoms are often ineffective or have intolerable side effects. Therefore, non-pharmacologic interventions are an attractive alternative. Exercise in particular has has the potential to alleviate the progressive impairment related to these non-motor symptoms. In this commentary, we explore available research addressing the impact of exercise and physical activity on autonomic dysfunction, cognitive impairment, and sleep disorders in Parkinson's disease, and suggest areas in need of further study. Many gaps remain in our understanding of the most effective exercise intervention for these symptoms, the mechanisms underlying exercise-induced changes, and the best way to monitor response to therapy. However, available research suggests that exercise is a promising approach to improve non-motor symptoms in patients with Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease diagnosed by its motor symptoms of bradykinesia, rest tremor, rigidity, and postural instability. In addition to these motor symptoms, patients with PD experience non-motor symptoms including autonomic dysfunction, cognitive decline, sleep disorders, and neuropsychiatric symptoms such as depression, anxiety, and psychosis(1). These non-motor symptoms adversely affect quality of life and can be even more disabling than the motor symptoms(2). Medications used to treat these symptoms are often inadequately effective and can cause intolerable side effects(3, 4). Therefore, patients, physicians, and researchers have developed increased interest in the potential of non-pharmacological therapies to treat non-motor symptoms in PD(5). For example, surgical therapies, such as deep brain stimulation (DBS), have been investigated for their influence on non-motor symptoms. An excellent recent review summarizes available evidence, which suggests that, in general, DBS can worsen

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Conflict of Interest Statement:

AA has no conflicts of interest related to this manuscript.

AM has no conflicts of interest related to this manuscript and has no disclosures.

performance within some cognitive domains and can improve other non-motor symptoms(6).

Another non-pharmacological therapy that has promise for improving non-motor symptoms is exercise. Exercise interventions have established efficacy for treating the motor symptoms of PD, with many different types of exercise activity, including stretching, walking, dance, tai chi, aerobic, resistance, and multimodal exercises showing beneficial effects on motor symptoms in PD(7). Based on research in the general population, exercise also has the potential to improve autonomic function, attenuate cognitive decline, and improve sleep and daytime sleepiness. In this commentary, we discuss the available evidence supporting the use of exercise for treatment of autonomic dysfunction, cognitive decline, and sleep disorders in patients with PD and suggest areas for future research.

AUTONOMIC DYSFUNCTION

Autonomic dysfunction in PD

Autonomic dysfunction (AutD) is common in PD, with reported prevalence ranging from 14 to 80%(8). It may include dysregulation of cardiovascular, gastrointestinal, urinary, pupillary, and thermoregulatory systems(9). AutD can occur at any stage of the disease, with gastrointestinal, urinary, and orthostatic symptoms increasing over time but notable in early and even premotor stages(10). As the disease progresses, AutD significantly impairs quality of life (QoL) in PD patients(1).

Cardiovascular Autonomic Dysfunction and Exercise

Sympathetic dysfunction is the major cause of cardiovascular dysregulation in PD, which occurs in at least 50% of patients(8). Cardiovascular AutD includes orthostatic hypotension (OH), supine hypertension, and increased resting heart rate(8, 11). These symptoms can be exacerbated by medications used to treat PD. Interestingly, the severity of OH does not necessarily increase with the duration of disease(11). In addition to negatively affecting QoL, OH increases fall risk, hospitalizations, and cost of care in PD(12).

Pharmacologic therapies for OH have limited efficacy and can be associated with serious side effects including exacerbation of supine hypertension and ventricular hypertrophy(8). Therefore, it is important to explore safe and effective non-pharmacological strategies for treatment of AutD. Exercise has potential to enhance autonomic regulation and this has been investigated in healthy adults. For example, a study of 17 healthy adults showed that regular exercise increases orthostatic tachycardia and cardiovagal baroreceptor sensitivity (BRS), which alleviates OH in the early phase post-exercise(13). Further, an aerobic training (stationary bike or treadmill) intervention over one year improved orthostatic tolerance in elderly participants in a small study (N=8)(14). Additionally, brief exercises can be used to control symptoms of OH. For example, a controlled study, which included 42 older patients, showed that participants who performed leg extension exercises against a resistance band had significantly less reduction in systolic blood pressure when compared to a bed rest control group, when given an orthostatic challenge(15). Despite these results, there are also potential risks of exercise on OH. For example, one study of older adults with OH due to

various co-morbidities failed to show improvement in orthostatic blood pressure in an 8-week home based resistance training program group(16) and another study of patients with chronic autonomic failure had exacerbation of OH with acute exercise(17). Therefore, studies of the influence of exercise on AutD in PD patients are needed to determine if this might be a meaningful treatment option for this patient group.

Only one randomized, controlled trial has been published addressing the effects of exercise on cardiovascular AutD in PD. This study assigned 30 PD patients to either resistance training or a control group for 12 weeks. PD participants in the training group had improved cardiac sympathetic modulation, as measured by heart rate variability and blood pressure response(18). No change in parasympathetic modulation was seen. The improvement in sympathetic modulation has potential to help reduce symptoms as well as cardiovascular morbidity and mortality in patients with PD(18). Additional studies regarding the role of exercise in PD patients are needed to better understand the underlying mechanisms involved in autonomic modulation.

Urinary Dysfunction and Exercise

Bladder dysfunction, including nocturia and increased urgency and frequency of micturition, is one of the most commonly reported symptoms of AutD in PD, affecting up to 93% of patients(8). These symptoms can inhibit social activity, disrupt sleep, and impair quality of life(8). To our knowledge, no studies to date have investigated the influence of traditional exercise on bladder dysfunction in PD. However, bladder training exercises have been investigated and shown to reduce urinary incontinence in PD(19). Therefore more studies are required to establish any role of exercise in treating urinary dysfunction in PD patients.

Gastrointestinal dysfunction and Exercise

In PD patients, autonomic impairment can occur along the entire length of the gastrointestinal (GI) tract, resulting in sialorrhea, dysphagia, impaired gastric motility, constipation, and bowel incontinence(20). These individual symptoms affect up to 70% of PD patients(20). In healthy adults, exercise is thought to improve constipation(21), but questions remain regarding effects of exercise on constipation in PD. One randomized, controlled pilot study, evaluated the effects of Qigong mediation movement exercises on constipation as a secondary outcome and found persistent benefit of the exercise over time in PD patients(22). Other autonomic symptoms, including urinary and sexual dysfunction, remained unchanged in both groups over time. To our knowledge, no other studies have yet evaluated the influence of exercise or increased physical activity on constipation in patients with PD and therefore more studies are required to determine the influence of exercise on GI symptoms.

COGNITIVE DYSFUNCTION

Cognitive Dysfunction in PD

Cognitive impairment has been recognized as a significant predictor of QoL in PD(23). Additionally, this non-motor symptom increases caregiver burden, leads to loss of productivity, and increases likelihood of institutionalization(23, 24). Cognitive deficits in PD

include executive dysfunction, memory deficits, language impairment, problems with visuospatial and visuo-constructive abilities, and mild cognitive impairment(25). At the time of diagnosis, up to 20% of PD patients have some degree of cognitive impairment(26) and up to 83% develop dementia within 20 years of motor symptom onset(27).

Cognitive Dysfunction and Exercise

Unfortunately, medications aiming to treat cognitive impairment in PD can have associated side effects and are not effective at slowing or stopping progression of cognitive decline(4). Therefore, it is important to evaluate the potential of different non-pharmacological therapies to improve cognition in PD. Exercise can improve cognitive function and attenuate cognitive decline in older adults(28). A recent meta-analysis of the effects of exercise on cognition in adults over age 50 showed significant improvements in multiple cognitive domains due to all modes of exercise reviewed (aerobic, resistance, multimodal, tai chi, yoga)(29). Relevant moderators of this effect were duration of session and intensity of exercise, with best effects for moderate to high intensity exercise of a duration of 45–60 minutes per session(29). At the structural level, exercise in older adults can increase hippocampal volume(30), suggesting the possibility of neuroprotective effects.

In PD, clinical trials investigating different exercise types, durations, and frequencies also demonstrate promise for exercise-induced improvements in cognitive function. For example, types of exercise interventions that have shown beneficial effects on cognition in PD include tango, aerobic exercise, combined resistance and aerobic exercise, and resistance training alone(31–36). Many of these studies included a control comparator group. For example, the effects of adapted tango on visuospatial function were investigated in a study in which 23 PD patients participated in 30 hours of adapted tango, compared to an educational control group. The patients in the tango group showed improvements in visuospatial function and motor symptom severity, while the control group did not improve(31). Another study investigated the effects of a low intensity passive cycling intervention on cognition in PD. In this intervention, 19 PD participants sat passively (without providing resistance) on a motorized bicycle that rotated the pedals at different rates. Passive cycling sessions occurred once per week for 4 weeks. Executive function, which was measured with Trail Making test A and B, improved following the intervention(32). Active aerobic exercise has also been studied in PD. A small study randomized 17 patients to a treadmill training intervention (45 minutes, 3 days per week for 4 weeks) or a control group and showed improvement in executive function in the treadmill group(33). Tanaka and colleagues assigned 20 mild to moderate PD patients to a control group or to 6 months of a multimodal exercise program that included moderate intensity aerobic exercise, 3 days per week. Participants in the exercise group showed improvement in executive function, as measured by the Wisconsin Card Sorting Test(34). Another study combined resistance and aerobic exercise and measured the effects on cognition in PD patients. Twenty-eight individuals with PD were assigned to either the exercise group (n=15) or a control group (n=13). Participants in the exercise group completed exercise two times per week for 12 weeks and showed improvement in executive function(35). A study by David and colleagues suggests that resistance exercise may also benefit cognition in PD patients. In this randomized clinical trial, eighteen PD patients participated in modified fitness counts (mFC) and twenty PD

patients in progressive resistance exercise training (PRET). The mFC group participants underwent stretching, balance and breathing exercises while PRET group participants underwent weightlifting exercises. This study showed that 24 months of PRET or mFC helps to improve attention and working memory in PD patients(36). This study poses an interesting possibility that the social aspect of an exercise intervention (i.e. more social engagement with study staff, trainers, and other participants than if the participant had remained at home) might contribute to cognitive improvement(36). Regardless, this compilation of studies provides a good rationale for the use of exercise to improve cognitive function in PD.

SLEEP DISORDERS

Sleep Dysfunction in PD

Sleep dysfunction is another common non-motor symptom in PD, affecting up to 98% of patients(37). Sleep disorders in PD include sleep fragmentation, insomnia, rapid eye movement (REM) sleep behavior disorder, excessive daytime sleepiness (EDS), periodic limb movements of sleep, and circadian rhythm dysregulation(38,39). PD patients also have alterations in sleep architecture, including reduced time spent in REM and slow wave sleep, which is important for memory consolidation and intellectual performance(40). Sleep symptoms negatively influence quality of life and EDS has the potential to impair safety and reduce independence(41, 42). Pharmacologic therapies are available for some sleep complaints in PD, but have potential for side effects(3). For example, soporific agents can impair balance and cognition and cause residual grogginess the next morning(43). Alerting agents can lead to tachycardia and weight loss(44). Therefore, non-pharmacologic therapy such as exercise is an attractive alternative for treatment of sleep dysfunction in PD.

Sleep Disorders and Exercise

In healthy older adults, both acute and chronic exercise interventions improve sleep. For example, meta-analyses have demonstrated that chronic exercise training increases sleep efficiency and total sleep time, reduces latency to sleep onset, and, in some studies, increases slow wave sleep(45, 46). Acute exercise reduces REM sleep and delays REM latency as well as increases total sleep time and slow wave sleep(47). Additionally, healthy older adults who undergo aerobic or resistance training report improved subjective sleep quality(48, 49).

Exercise has shown promise for improving sleep in patients with PD as well. There are only a few randomized controlled trials (RCTs) evaluating sleep as an outcome due to an exercise intervention in PD. In one such study, Nascimento and colleagues evaluated 42 PD patients (23 in the exercise group and 19 in the control group) with the Mini-Sleep Questionnaire before and after a 6-month, multimodal exercise intervention, which included aspects of resistance, aerobic, and balance training(50). The investigators found a significant improvement in sleep quality in the exercise group relative to the control group(50). In another RCT, Silva-Batista and colleagues randomized 22 patients to resistance training or a no-exercise control for 12 weeks, with 2 sessions per week(51). They used the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality before and after the intervention between the groups and also compared PD participants to healthy control participants who did not

exercise. Although at baseline the PD participants had worse sleep quality than healthy controls, the resistance training PD group demonstrated improvement in sleep quality, and at the end of the intervention had better sleep quality scores than control participants. This improvement was correlated with improvement in muscle strength. The control PD group did not show any change in sleep quality(51). Another RCT employed a Baduanjin Qigong meditative movement intervention, randomizing 100 PD patients to Qigong and walking or a walking-only control. The Qigong group had improvement in sleep quality, as measured by the Parkinson's Disease Sleep Scale (PDSS)-2, while the control group did not improve(52). A recent study compared individual (N=15) versus group (N=15) exercise plus chronic disease self-management (CDSM) in a group of PD patients with depression. In this study, depression was the primary outcome and improved equally in both groups. Sleep quality and daytime sleepiness were measured as secondary outcomes in the combined groups (N=30) with the Scales for Outcomes in Parkinson's Disease (SCOPA)-sleep, and did not show improvement(53). A small study evaluated the influence of physiotherapy compared to active theater on motor and non-motor symptoms in PD with a three-year intervention. The sleep-related outcome was daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS), which showed more improvement in the active theater group compared to the physiotherapy group(54).

Non-randomized studies and uncontrolled studies have also been performed to investigate the influence of exercise on sleep in PD. One retrospective study investigated the PDSS before and after a rehabilitation program. Eighty-nine patients completed the program 3 times a day, 5 days per week for 28 days and were compared to a control group of 49 patients who did not receive the intervention. The rehabilitation group showed significant improvement in sleep quality, while the control group did not improve(55). A pilot study investigated the influence of exercise on quality of life in 20 PD patients. The intervention employed a combined strength training/aerobic protocol 3 days per week over 12 weeks. Quality of life was measured with the Nottingham Health Profile, which includes some questions about sleep. PD participants showed a trend toward improvement in sleep quality after this exercise intervention(56). Finally, Wassom and colleagues investigated the influence of 6 weeks of Qigong exercises on sleep and gait in 7 PD patients. After the intervention, participants had a trend toward improvement in the PDSS-2(57). Taken together, these studies indicate that many different types of exercise can improve subjective sleep quality in PD.

DISCUSSION

Exercise is a beneficial, cost effective, low risk intervention that improves overall health and provides promise for improving both motor and non-motor symptoms in PD. In this commentary, we discuss that, although additional study is needed, exercise interventions of several different modalities and durations demonstrate potential for improvement of cognitive dysfunction and sleep disorders. To delineate the impact of exercise on autonomic function, more randomized, controlled trials are needed.

Several factors specific to patients with PD should be considered when recommending an increase in physical activity. For example, certain symptoms experienced by PD patients

might prevent active engagement in physical exercise. These factors include motor symptoms and risk of falls; excessive daytime sleepiness; depression, which decreases self-esteem and self-efficacy (58); apathy; and cardiac sympathetic denervation, which can be associated with fatigue(59). Any of these symptoms can reduce participation in physical activity and contribute to a more sedentary lifestyle among PD patients(60). Strategies to improve participation include development of community-based programs, identifying and treating symptoms, such as depression, that might affect compliance to an exercise program, adapted interventions (i.e. seated exercises) to accommodate motor symptoms, and discussing barriers to exercise with the patient and caregiver. Further, an increased understanding of the beneficial effects of exercise on both motor and non-motor symptoms has the potential to increase enthusiasm for participation.

Areas in Need of Future Research

While the majority of studies suggest that exercise promotes improvements in non-motor symptoms in PD, there are many questions that remain unanswered. For example, the ideal modality, session duration, and frequency of exercise for the best improvement in each non-motor symptom, or even for motor symptoms, are not known. Although head-to-head comparisons of different exercise parameters may be difficult, it is possible that biomarkers for improvement in non-motor symptoms can be identified that will allow for monitoring of efficacy of different exercise interventions in smaller groups of patients. Whether such biomarkers will be derived from body fluids (i.e. blood, cerebrospinal fluid, saliva, urine), neuroimaging or clinical measures, or a combination of markers has yet to be determined. These measures could also be used to investigate longitudinally whether physical activity might alter the course of PD or its symptoms.

Other potential areas of investigation include determination of factors that may predict responsiveness to exercise and its effects on non-motor symptoms. These features could include baseline levels of fitness; comorbid conditions; underlying motor symptoms of PD; baseline cognitive function, sleep quality, mood, or autonomic function; pre-morbid activity levels; trophic factors; degree of inflammation; and as yet unknown factors. Additionally, potential mechanisms underlying exercise-induced changes in non-motor symptoms need to be investigated. Another important consideration is that there are possible factors relevant to PD that may not be as important in the general population that could make PD patients more susceptible to improvements due to exercise. For example, exercise can alter dopamine receptor availability in humans and in animal models of PD, which could have downstream effects on motor and non-motor symptoms(61,62). Structural and functional imaging studies to investigate changes due to exercise interventions could provide additional insight to these underlying mechanisms.

To better address knowledge gaps related to the effects of exercise on cognition, research studies exploring the impact of different exercise modalities on specific cognitive domains may ultimately help to tailor exercise prescriptions to individual patient needs. Regarding autonomic dysfunction, more and larger studies are needed to delineate the beneficial effects as well as the potential risks of exercise on orthostatic hypotension, urinary dysfunction, and GI symptoms. Specific to sleep disorders, while evidence demonstrates efficacy of exercise

to improve subjective sleep quality, to our knowledge there are no published studies on how exercise influences objective sleep outcomes, as measured by polysomnography or even actigraphy monitoring, in PD. These outcomes need to be investigated to develop a complete understanding of exercise-induced effects on sleep and vigilance. Further, the influence of exercise on circadian rhythms and the influence of time of day of exercise on sleep in PD are not known. These and other unanswered questions in combination with the promise of therapeutic efficacy of exercise on multiple different aspects of motor and non-motor symptoms in PD make exercise interventions an exciting area of research.

Acknowledgments

This work is supported by the National Institutes of Health, NINDS K23NS080912 (AWA) and the Parkinson's Disease Foundation.

She receives grant funding from the NIH NINDS (K23 NS080912), Parkinson's Disease Foundation, the Rehabilitation Research Resource to Enhance Clinical Trials (1P2CHD086851), National Institute on Aging (P30 AG022838), and the Center for Clinical and Translational Science (UL1 TR00141), and is an investigator for studies sponsored by the Michael J. Fox Foundation for Parkinson's Research, Roche, Jazz Pharmaceuticals, Axovant Sciences, Ltd., and Abbvie. She served on an advisory board for Jazz Pharmaceuticals.

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