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Review Article

Effectiveness of Exercise on Reducing Fatigue in Parkinson's Disease: A Systematic Review

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Abstract

Purpose: Parkinson's disease (PD) is characterized by motor and nonmotor symptoms, such as bradykinesia, rigidity, fatigue, and cognitive impairments etc. Fatigue is one of the most debilitating symptoms, and voted as the leading symptom in need of research by patients with PD. However, there is a lack of effective treatment for PD-fatigue. Limited evidence suggests that exercise training improves fatigue in PD. The purpose of this systematic review was to evaluate the effectiveness of exercise program on reducing fatigue in patients with PD.

Methods: A systematic search of databases CINAHL Complete, PubMed, and PEDro (Physiotherapy Evidence Database) was performed using terms: "Parkinson's disease" AND ("exercise" OR "physical therapy" OR "physical activity") AND "fatigue". To be included in this review, the studies had to be randomized controlled trials, and to meet the following criteria: 1) examining patients with PD; 2) using exercise training such as aerobic exercise, treadmill training, or exergaming etc.; 3) having fatigue as an outcome measure; and 4) at least 4 out of 10 on the PEDro scale.

Results and Discussion: Seven randomized controlled trials published between 2012 and 2017 were included in this review. Six of the seven studies demonstrated statistically significant reductions in fatigue following exercise programs. This review showed that multiple modes of exercise interventions were effective in reducing PD-related fatigue.

Conclusions: Exercise program may be effectively utilized as an integral component of clinical management of PD-related fatigue and other symptoms, ultimately maximizing the quality of life in patients with PD.

Keywords: *Parkinson's Disease; Fatigue; Exercise; Physical Therapy; Effectiveness*

Abbreviations

FSS: Fatigue Severity Scale; LSVT: Lee Silverman Voice Training; MFIS: Modified Fatigue Impact Scale; MS: Multiple Sclerosis; PD: Parkinson's Disease; PEDro: Physiotherapy Evidence Database; RCT: Randomized Controlled Trial

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease due to a loss of dopamine-producing neurons in the basal ganglia [1,2]. PD is clinically characterized by both motor and nonmotor symptoms: including bradykinesia, rigidity, tremor, and anxiety, fatigue, sleep disorders, heath-related quality of life etc [3,4]. Individuals with PD frequently report that fatigue is one of the most debilitating symptoms associated with PD. And fatigue has been voted the number one symptom in need of research by patients with PD [5,6]. Although fatigue has a significantly negative impact on quality of life in patients with PD, there is a lack of effective treatment for PD-related fatigue as anti-PD medication shows equivocal results in combating this non-motor symptom [7-9].

Fatigue is a common symptom of a variety of neurological disorders such as multiple sclerosis (MS), stroke, and poliomyelitis [10]. Exercise interventions have been shown to be effective in combating fatigue associated with progressive neurological disorders. A 20-week stepwise physical activity program focused on gradual stretching, resistance, and aerobic exercise for patients with MS demonstrated significant decreases in measures of fatigue severity [11]. Dalgas., *et al*. [12] examined the effect of exercise on MS-associated fatigue by randomly assigning 54 patients with MS to 15-week aerobic training or a non-exercise condition. The results demonstrated that the group receiving exercise had a significant reduction in fatigue.

Limited evidence suggests that exercise can potentially reduce PD-related fatigue [13]. The objective of this systematic review study was to evaluate the effectiveness of specific type of exercise therapy compared with conventional care on management of fatigue in patients with Parkinson's disease.

Materials and Methods

This systematic review followed the PRISMA (preferred reporting items for systematic reviews and meta-analyses) criteria [14].

Inclusion and Exclusion Criteria

Types of the Study

To be included in this review, a study had to be conducted using a randomized controlled trial (RCT), and had a score of at least 4 out of 10 on the scale of Physiotherapy Evidence Database (PEDro scale) [15].

Types of Participants

Only studies examining participants diagnosed with idiopathic PD were included in this review. In addition, the studies with participants treated by deep brain stimulation were excluded.

Types of Interventions

This review included RCTs that examined exercise intervention, such as treadmill walking, aerobic training, Lee Silverman Voice Training (LSVT BIG therapy), and Argentine tango therapy. Clinical trials assessing effects of dopaminergic medication on fatigue were excluded from this review.

Types of Outcome Measures

The study was included if outcome measures included fatigue. Measurement tools were Modified Fatigue Impact Scale (MFIS), Parkinson Fatigue Scale (PFS), and Fatigue Severity Scale (FSS) all of which sustain measures of fatigue [16-18].

Search strategies

A systematic search of CINAHL Complete, PubMed, and PEDro was administered to obtain published studies until October 2017. A manual search was also performed by checking the references of the eligible studies. Specific search terms and keywords with the subject heading were utilized. The following keywords were used in the search:

- "Parkinson's Disease" OR "Parkinson"

  AND

- "Physical Therapy" OR Exercise OR "Physical Activity"

  AND

- "Fatigue"

Data Collection and Analysis

Selection of Studies/Screening

Two reviewers (SM and MH) independently screened the articles based on the titles and abstracts to determine whether they met the inclusion criteria. After screening the abstract and titles, two reviewers completed a full text analyses of the articles to determine if each study met the inclusion and exclusion criteria, followed by a third reviewer (RX) to review all full text articles for verification. Relevant data were extracted from articles that met the inclusion criteria. Table 1 lists the study design, sample size, interventions, outcomes, and PEDro scores of the seven included studies.

Authors	Year	Study Design	Participants (N)	Intervention (Experimental)	Comparative Intervention	Outcome Measures	PEDro scale
Canning., *et al*.	2012	RCT*	N = 20	Semi-supervised home based Treadmill Walking	Usual Care- advice to maintain current level of physical activity	Modified Fatigue Impact Scale (MFIS)	8/10
Cugusi., *et al*.	2015	RCT	N = 20	12-week Nordic Walking program	Conventional care	Parkinson's Fatigue Scale	4/10
Dashtipour., *et al*.	2014	RCT	N = 11	Lee Silverman Voice Training (LSVT) BIG Therapy	General Exercise	MFIS	5/10
Ribas., *et al*.	2017	RCT	N = 20	Exergaming	Conventional Exercise	Fatigue Severity Scale (FSS)	7/10
Romenets., *et al*.	2014	RCT	N =33	Argentine tango partnered classes	Self-directed exercise group	FSS	6/10
Uc., *et al*.	2015	RCT	N = 60	Continuous Training of aerobic walking	Interval Training of aerobic walking	FSS	5/10
Winward., *et al*.	2012	RCT	N =39	12-week Community Exercise Program	Conventional care	FSS	8/10

Table 1: *Characteristics of the included study.*

** RCT: Randomized Controlled Trial*

Assessment of Methodologic Rigor

All included articles were assessed using PEDro scale which is a tool for evaluating and quantifying methodologic quality of clinical trials. The PEDro scale is utilized to assist the reviewers in determining the construct validity and internal validity of included studies, and inclusion of statistically significant data to make results interpretable of each study. In addition, external validity was also assessed (Criterion 1), but this criterion is not included in final count of the PEDro score [15].

Results and Discussion

Study Selection

The initial search of databases and other sources resulted in a total of 916 articles with 63 articles remaining after a thorough screening of titles and abstracts. The 56 articles were determined to be ineligible, as they did not include exercise program but pharmacologic regimen, did not measure fatigue as an outcome, nor utilized an RCT design. Ultimately, seven articles met the inclusion and exclusion criteria, and were thus included in this review [19-25]. Figure 1 is a flowchart illustrating the selection process of the articles for this study.

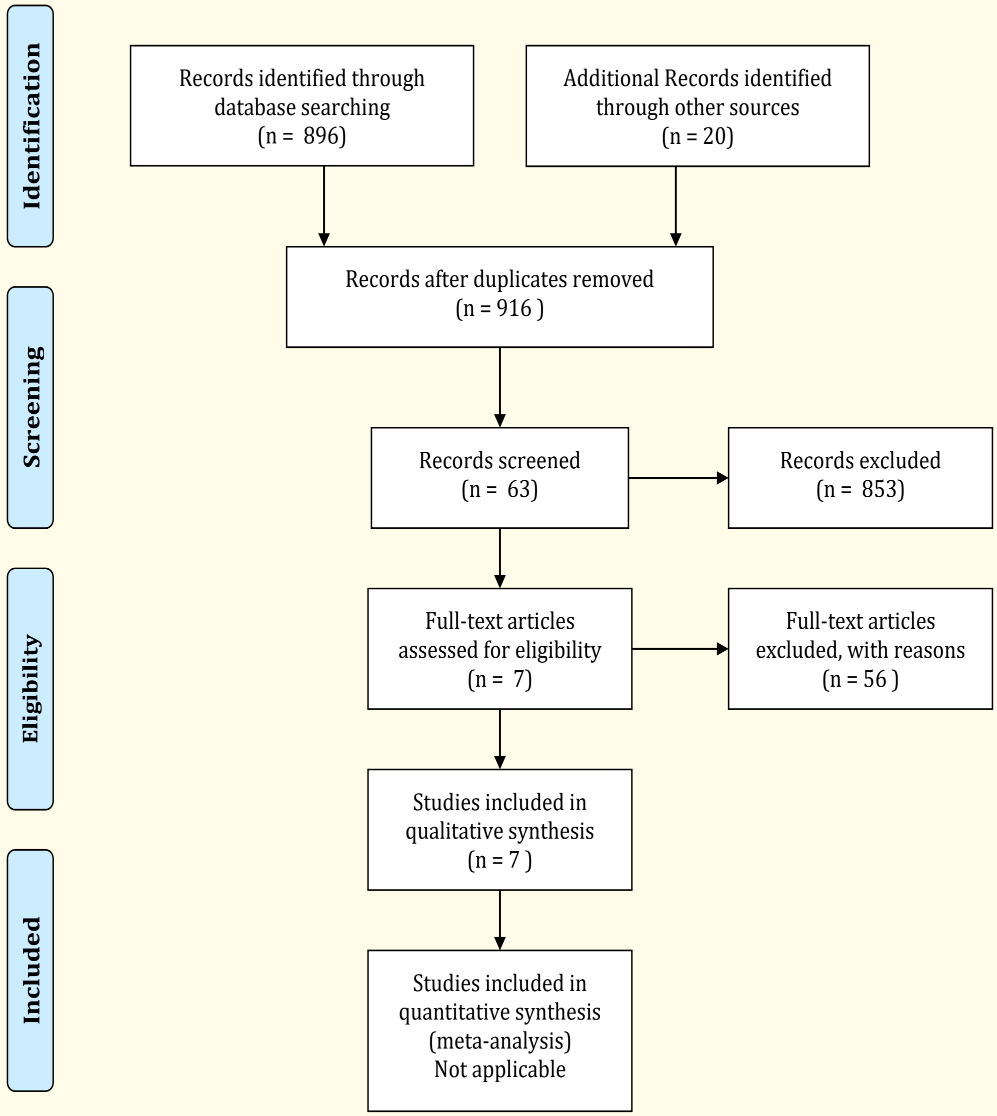

Figure 1: *PRISMA flowchart: Study Selection Process.*

Study Characteristics

The included studies were published between 2012 and 2017, and were randomized control trials with the control group also receiving treatment. Of the seven studies, six reported improvements in fatigue after the exercise interventions.

Most of the interventions included some type of aerobic exercise, resistance, balance, and home-based treadmill walking program. A few studies focused on more specific aspects of exercise, including a Nordic Walking program [20], Exergaming [22], Argentine tango therapy [23], and LSVT BIG therapy [21].

Outcomes

Canning., *et al*. [19] showed significant improvement in fatigue in the group receiving home-based treadmill training ($p < 0.05$). Nordic Waling was found to significantly ($p < 0.05$) reduce fatigue [20]. Dashtipour., *et al*. [21] reported statistically significant improvements in the MFIS score at 6-month posttests for both LSVT BIG and General Exercise groups ($p < 0.05$). Uc., *et al*. [24] reported a significant improvement in the Fatigue Severity Scale upon continuous training of aerobic walking ($p < 0.01$). Ribas., *et al*. [22] found that Exergaming had significantly improved fatigue ($p < 0.05$). Modest borderline improvements in the FSS ($p < 0.057$) were demonstrated by participation in 1 hour sessions of traditional Argentine tango twice weekly for 12 weeks [23]. On the other hand, Winward., *et al*. [25] found no significant changes in fatigue between the two groups in response to a community gym-based exercise program and conventional care ($p = 0.76$) or from baseline to 3-month posttest.

This systematic review aimed to examine the effectiveness of exercise and physical activity on treatment of fatigue in PD. Physical activity and its effect on PD-fatigue is an understudied topic of research. Of the 7 articles that met the review criteria, six demonstrated significant improvements in fatigue levels.

Fatigue has long been recognized in other neurological conditions including MS, stroke, and poliomyelitis [10]. Effects of exercise therapy has relatively been well studied and proven to be effective in managing fatigue associated with MS [26-28]. Aerobic exercise has been most studied regarding its effects on the neuronal connections and on reducing fatigue in MS. Progressive resistance training targeted toward lower limb musculature in patients with MS has been found to decrease levels of fatigue by increasing muscular endurance [26]. Heine., *et al*. [27] shows that endurance exercise training has a neuroprotective effect, and can induce physiological and psychological changes that counteract the impact of fatigue in patients with MS. Considering that exercise has been demonstrated to reduce fatigue in other neurodegenerative disease, it is plausible to expect that exercise therapy plays a role in reducing fatigue in patients with PD.

In addition, Pavese., *et al*. reported an association of fatigue in PD with altered transmission of serotonin through the striatal and limbic pathways [29]. Both groups of subjects with PD (one group with fatigue and the other without fatigue) underwent imaging protocols using ^{18}F-dopa and ^{11}C-DASB, biomarkers of dopamine storage capacity and serotonin transporter availability. None had experienced depression or sleep disturbance. Results showed that subjects with PD-fatigue had significantly lower serotonin transporter binding than did subjects without fatigue. Authors concluded that PD-fatigue is associated with reduced serotonergic function in the basal ganglia and limbic structures as well as potentially with insular dopaminergic dysfunction. The findings implied that strategies to increase brain level of serotonin would be a rational approach for relieving fatigue symptom in Parkinson's disease [29]. Exercise program has been demonstrated to increase serotonin synthesis and function of the brain in mental disorders such as depression as well as several rodent studies [30]. Prescription of an exercise program in patients with PD-fatigue has the potential to enhance serotonin transmission within the involving areas of the brain, and can therefore decrease fatigue.

Overall, exercise has been shown to have a neuroprotective effect and enhance neuroplasticity [31]. The included studies in this review investigated various types of exercises in regards to the treatment of non-motor symptoms of PD including fatigue. Six of the seven studies showed positive effects of exercise on PD-fatigue, except for the study by Winward., *et al*. showing that a 12-week gym-based workout that incorporated treadmill training and was largely self-determined, did not result in significant changes in fatigue. Participants' attendance was attributed to be one of the reasons [25]. In particular, research has also demonstrated five interactions of exercise and neuroplasticity: 1) intensity level directly affects plasticity, 2) the greater the complexity of the action, the greater the adaptation, 3) rewarding activities increase greater dopamine levels and enhance learning, 4) dopaminergic neuron activity and the amount of exercise are closely related, and 5) exercise as treatment in early stage of PD can slow the disease progression [32].

Limitations of the Review

The research articles reviewed in this study had limited sample sizes and primarily focused on motor symptoms of PD. The sample sizes in these research articles ranged from 11 to 60, given that research on efficacy of exercise in management of PD-related fatigue is still merging. The studies included in this review varied in the type of intervention, duration of treatment, and different measures of fatigue: MFIS, FSS, and PFS, due to an understudied topic. No meta-analysis was performed in this systematic review since intervention varied among included studies, and no original data were available. It is also acknowledged that publication bias may exist as only articles in English were included in this review.

Conclusion

This systematic review suggests that exercise program may be an integral part of treatment of PD-related fatigue and a tailored exercise program may be more effective in reducing fatigue in patients with PD compared to conventional therapy. More evidence is needed to elucidate the efficacy of exercise intervention and to guide clinical practice in management of fatigue and other debilitating symptoms in PD.

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None.

Conflict of Interest

Authors of this study have no financial interest or conflict of interest.

Bibliography

1. Galvan Adriana and Thomas Wichmann. "Pathophysiology of Parkinsonism". *Clinical Neurophysiology* 119.7 (2008): 1459-1474.
2. Fahn Stanley. "Description of Parkinson's Disease as a Clinical Syndrome". *Annals of the New York Academy of Sciences* 991 (2003): 1-14.
3. Gallagher David A., *et al*. "What Are the Most Important Nonmotor Symptoms in Patients with Parkinson's Disease and Are We Missing Them?" *Movement Disorders* 25.15 (2010): 2493-2500.
4. Lindqvist Daniel., *et al*. "Non-Motor Symptoms in Patients with Parkinson's Disease - Correlations with Inflammatory Cytokines in Serum". *PLoS ONE* 7.10 (2012): e47387.
5. Friedman Joseph H., *et al*. "Fatigue in Parkinson's Disease: A Review". *Movement Disorders* 22.3 (2007): 297-308.
6. Kluger Benzi M., *et al*. "Parkinson's Disease-Related Fatigue: A Case Definition and Recommendations for Clinical Research". *Movement Disorders* 31.5 (2016): 625-631.
7. Barone Paolo., *et al*. "The PRIAMO Study: A Multicenter Assessment of Nonmotor Symptoms and Their Impact on Quality of Life in Parkinson's Disease". *Movement Disorders* 24.11 (2009): 1641-1649.
8. Dogan Vasfiye Burcu., *et al*. "Independent Effect of Fatigue on Health-Related Quality of Life in Patients with Idiopathic Parkinson's Disease". *Neurological Sciences* 36.12 (2015): 2221-2226.
9. Elbers RG., *et al*. "Interventions for Fatigue in Parkinson's Disease (Review)". *Cochrane Database of Systematic Reviews* 10 (2015): CD010925.
10. Chaudhuri Abhijit and Peter O Behan. "Fatigue in Neurological Disorders". *Lancet* 363.9413 (2004): 978-988.
11. Fragoso Yara Dadalti., *et al*. "The Positive Effects of a Physical Activity Program for Multiple Sclerosis Patients with Fatigue". *NeuroRehabilitation* 23.2 (2008): 153-157.
12. Dalgas U., *et al*. "Fatigue, Mood and Quality of Life Improve in MS Patients after Progressive Resistance Training". *Multiple Sclerosis* 16.4 (2010): 480-490.
13. Lou Jau Shin. "Fatigue in Parkinson's Disease and Potential Interventions". *NeuroRehabilitation* 37.1 (2015): 25-34.

14. Moher D., *et al*. "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement". *Annals of Internal Medicine* 151.4 (2009): 264-269.

15. de Morton Natalie A. "The PEDro Scale Is a Valid Measure of the Methodological Quality of Clinical Trials: A Demographic Study". *Australian Journal of Physiotherapy* 55.2 (2009): 129-133.

16. Fisk JD., *et al*. "Measuring the Functional Impact of Fatigue: Initial Validation of the Fatigue Impact Scale". *Clinical Infectious Diseases* 18.1 (1994): S79-S83.

17. Brown RG., *et al*. "The Parkinson Fatigue Scale". *Parkinsonism and Related Disorders* 11.1 (2005): 49-55.

18. Herlofson K and JP Larsen. "Measuring Fatigue in Patients with Parkinson's Disease - the Fatigue Severity Scale". *European Journal of Neurology* 9.6 (2002): 595-600.

19. Canning Colleen G., *et al*. "Home-Based Treadmill Training for Individuals with Parkinson's Disease: A Randomized Controlled Pilot Trial". *Clinical Rehabilitation* 26.9 (2012): 817-826.

20. Cugusi Lucia., *et al*. "Effects of a Nordic Walking Program on Motor and Non-Motor Symptoms, Functional Performance and Body Composition in Patients with Parkinson's Disease". *NeuroRehabilitation* 37.2 (2015): 245-254.

21. Dashtipour Khashayar., *et al*. "Effect of Exercise on Motor and Nonmotor Symptoms of Parkinson's Disease". *Parkinson's Disease* (2015).

22. Ribas Camila Gemin., *et al*. "Effectiveness of Exergaming in Improving Functional Balance, Fatigue and Quality of Life in Parkinson's Disease: A Pilot Randomized Controlled Trial". *Parkinsonism and Related Disorders* 38 (2017): 13-18.

23. Romenets Rios Silvia., *et al*. "Tango for Treatment of Motor and Non-Motor Manifestations in Parkinson's Disease: A Randomized Control Study". *Complementary Therapies in Medicine* 23.2 (2015): 175-184.

24. Uc EY., *et al*. "Phase I/II Randomized Trial of Aerobic Exercise in Parkinson Disease in a Community Setting". *Neurology* 83.5 (2014): 413-425.

25. Winward Charlotte., *et al*. "Weekly Exercise Does Not Improve Fatigue Levels in Parkinson's Disease". *Movement Disorders* 27.1 (2012): 143-146.

26. Dodd KJ., *et al*. "Progressive Resistance Training Did Not Improve Walking but Can Improve Muscle Performance, Quality of Life and Fatigue in Adults with Multiple Sclerosis: A Randomized Controlled Trial". *Multiple Sclerosis* 17.11 (2011): 1362-1374.

27. Heine Martin., *et al*. "Exercise Therapy for Fatigue in Multiple Sclerosis". *Cochrane Database of Systematic Reviews* 9 (2015): CD009956.

28. Halabchi Farzin., *et al*. "Exercise Prescription for Patients with Multiple Sclerosis; Potential Benefits and Practical Recommendations". *BMC Neurology* 17.1 (2017): 185.

29. Pavese Nicola., *et al*. "Fatigue in Parkinson's Disease Is Linked to Striatal and Limbic Serotonergic Dysfunction". *Brain* 133.11 (2010): 3434-3443.

30. Young Simon N. "How to Increase Serotonin in the Human Brain without Drugs". *Journal of Psychiatry and Neuroscience* 32.6 (2007): 394-399.

31. Goodwin Victoria A., *et al*. "The Effectiveness of Exercise Interventions for People with Parkinson's Disease: A Systematic Review and Meta-Analysis". *Movement Disorders* 23.5 (2008): 631-640.

32. Fox Cynthia M., *et al*. "The Science and Practice of LSVT/LOUD: Neural Plasticity-Principled Approach to Treating Individuals with Parkinson Disease and Other Neurological Disorders". *Seminars in Speech and Language* 27.4 (2006): 283-299.

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