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EXERCISE PARAMETERS FOR REDUCING FATIGUE IN PATIENT WITH IDIOPATHIC PARKINSON'S DISEASE – SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: -

Background: Very few studies have shown their effectiveness on fatigue or in any other non-motor symptoms in Parkinson's Disease. This remains controversial and difficult in choosing the treatment protocol which has been not the same among various therapists. **Objective: -** The purpose of this systematic review is to explore the exerciseparameters and express the need for non-invasive biomarkers for fatigue.**Methods: -**A total of 2302 articles from the Electronic databases from Jan 2010 to Jan 2021 were extracted. After applying the eligibility criteria 7 RCT studies were considered. **Results: -** 5 RCTs were reported until now with an average of 5.8 out 10 on the PEDro scale. None of the studies used any type of biomarker as an objective outcome measure for analysing fatigue.**Conclusion:** -Exercise interventions have proven to be the best source of reduction of fatigue in Parkinson's disease. But very fewer studies have been done, where enough data are unable to reproduce them in another setting. Hence, there is an extensive need to conduct more Randomized control trials with feasible non-invasive Biomarker the evaluate the treatment progression

Keywords: - Physical Therapy rehabilitation, biomarker,fatigue, Parkinson's Disease

Introduction: -

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Fatigue though existed long since the discovery of Parkinson's disease, has recently been diagnosed as a common problem among the patients with Parkinson's disease with 35%- 75% [(1)]. Fatigue has been reported as a nightmare and the worst debilitating symptom by patients which often goes unattended by therapists and neurologists as a consequence of varied motor and non-motor symptomsin the Indian population [(2)]. There have been minimal or no evidence-based studies on the physiological and biochemical analysis to measure fatigue, proving the efficiency of exercise [(3)]. With limited research on its pathophysiology and interventions, fatigue has been an element to resist the recovery process in the patients [(1,4)]. A prevalence study done by Friedman and Friedman showed that 68% have reported having fatigue, which was different from the fatigue they experienced before getting diagnosed with Parkinson's disease [(5)].

A study at university movement disorder with 75 patients with Parkinson's Disease showed that fatigue, pain, imbalance, bradykinesia, and tremor were the most difficult symptoms which made the patients give up upon the previously enjoyed activities. The patients with deep brain stimulation also showed that fatigue significantly impacts the quality of life [(6)]. Fatigue has been reported as one of the first prodromal symptoms in the early subclinical stages of the disease, by the time patients were diagnosed they started showing motor symptoms which masked the fatigue-related symptoms anddisability [(7)].

Central and peripheral fatigue are the two elements that affect functional ability, quality of life, and loads strain on the caregivers. There is no specific definition for fatigue, but it has been referred to as the feeling of tiredness, weakness or lack of energy to start an activity, lack of concentration, and memory impairment. It has also been shown that fatigue, apathy, depression, and sleep disorders are independent aspects occurring in Parkinson's disease [(8,9)].

Fatigue is described as the primary manifestation of the disease, there is a hypothesized pathophysiology explaining as altered hypothalamic – pituitary -adrenal axis (HPA),involvement of basal ganglia – cortical mechanism- frontal loops imbalance between neurotransmitter as dopamine and serotonin, neuroinflammation and cardiac sympathetic denervation. Lack of insight into a standardized definition, pathophysiological mechanisms, and its multifactorial nature have created barriers for developing an effective treatment intervention [(10)].

However, in the literature review, there are no robust parameters mentioned which can be used universally. The current conceptual line in physiotherapy postulate that intensive multi-

modal exercise regimes could alleviate fatigue-related symptoms which is an alarming disability concern for the patient. Fatigue is a perceived symptom hence there arises the need for biomarkers to quantity fatigue levels.

The purpose of this study is to systematically analyse the evidence-based literature for the possible treatment parameters in terms of duration, frequency, and intensity for fatigue in Parkinson's disease and address the need for non-invasive biomarkers like salivary cortisol levels to evaluate the treatment prognosis.

Method: -

Literature articles from Jan 2000 to Jan 2021 were searched using keywords as fatigue,physical therapy interventions, physiotherapy, rehabilitation, Parkinson's disease systematically analyzed with PRISMA guidelines PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) assumptions and principles for systematic reviews were followed. The PRISMA statement is inclusive of a 27-item checklist with a four-phase flow diagram. The aim of the PRISMA statement aims to help authors improve the reporting of systematic reviews and meta-analysis

The literature articles were obtained from CINHAL, Scopus, Cochrane, Elsevier, Science Direct, and PubMed. The methodological quality was assessed by the Physiotherapy Evidence Database (PEDro) tool, data were extracted based on selection criteria provided. While using the PEDro tool each article was rated over an 11- item scale, the first item was a measure of external validity thus was excluded while scoring finally which totalled to 10. The tool is reliable and valid to assess the quality of each study.

The studies included were analysed tabulated the following items: methodology quality, sample characteristics, outcome measures, methodology design, intervention parameters, and intervention results

The keywords used were combined as Parkinson's disease AND Fatigue AND Exercise, Parkinson's disease AND Fatigue AND Exercise AND Fatigue Biomarker, Parkinson's disease AND Fatigue AND Therapy, Parkinson's disease AND Fatigue AND balance exercises, Parkinson's disease AND Fatigue AND Cardiovascular exercises, Parkinson's disease AND Fatigue AND Resistance training.

Eligibility criteria: -

Inclusion criteria: -The inclusion criteria were articles published in English, studies that involved interventions for fatigue, Randomized control trials, samples were taken were only Parkinson's disease, all age group, all stages in Hoehn and Yahr scale.

Exclusion criteria: -The study excluded articles from which were other languages, conditions other than neurological ailments, Review articles, meta-analyses, systematic analysis, study protocols, and editorials.

The risk of bias was assessed using the Cochrane Risk of Bias. It evaluated seven sources of bias including randomization, allocation concealment, blinding, of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective, outcome reporting, and other potential bias and evaluated as being low risk, high risk, or unclear risk.

Fig: -1 Flowchart representing the process of database search

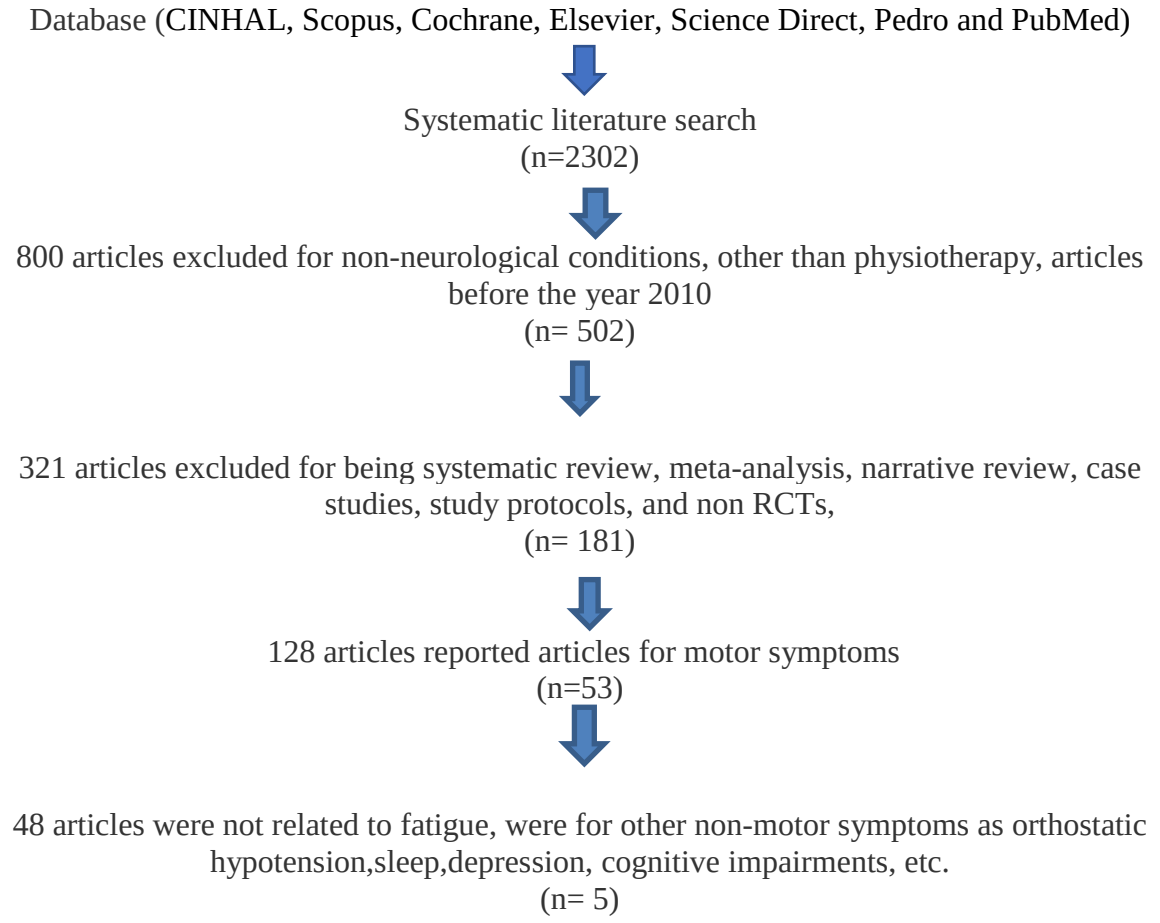

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Table 1: - Demographic details of the patients in the RCT studies.

Author	Year	number of participants	Age	Stage	Disease duration	Gender ratio	Fatigue measurement Score at baseline
Ghahari, S et al	2010	95	23- 90 above	-	11.4 years	Male = 18 Female = 77	FSS = 4
Winward et al	2011	39	18 and above	0-4	5.79 years	Male= 31 Female = 8	FSS = 4
Canning et al	2012	20	30 – 80 years	1-2	6.1 years	Male =11 Female =9	VAS 7 point= 3/4
Shulman, L. M et al	2013	67	40 years above	1-3	1- 18 year	Male = 50 Female = 17	-
Amirabas Abasi et al	2020	24	63 years and above	1-4	3.75 years	Male= 10 Female = 14	MFIS >/= 45

Table 2: - Details of the physical therapy interventions and treatment parameters are specified

Author Year	Exercises			Treatment parameters	Outcome measures	Results
Ghahari, S et al	Intervention group Group A Fatigue self-management group the importance of rest, communication, body mechanics, rearranging activity stations, setting priorities standards, and balancing a schedule	Intervention group Information-only group online information was provided	Control group Control group no intervention	7-week online program Weekly	Fatigue Impact Scale, Activity Card Sort Personal Wellbeing Index.	Fatigue improved but not significantly
Winward et al	Supervised community gym-based program – 5 * 30- minute aerobic sessions 2 strength sessions per week	-	Standard care	30 - 45 min (total) 15 to 20 min of cardiovascular fitness muscle strength and flexibility	Physical Activity Scale for the Elderly 2-minute walk Parkinson's Disease Questionnaire Summary Index [PDQ-SI Fatigue	Fatigue did not improve

					Severity Scale	
Canning et al	semi-supervised home-based program of treadmill walking	-	Advice is given to maintain the current activity levels	20–40 minutes, four times a week for six weeks	6-minute walk test distance VAS score	Fatigue improved
Shulman, L. M et al	A higher-intensity treadmill exercise	a lower-intensity treadmill exercise	stretching and resistance [leg press, leg extension, and curl].	30 minutes at 70%-80% of heart rate reserve 50 minutes at 40%-50% of heart rate reserve 2 sets of 10 repetitions on each leg on 3 resistance machines 3/wk, 3 months	6-minute walk $\dot{V}O_2$ 1-repetition maximum strength	Gait speed, $\dot{V}O_2$, Muscle strength improved No improvement in non-motor symptoms-fatigue
Amirabas Abasi et al	vestibular rehabilitation exercises -firm surface, foam, -balance board EC - EO -head movements to the sides, up-down; -throwing and catching a ball with walking exercises movement of the head; -moving a ball in hands from side to side. -Oculomotor exercises		control group -five minutes of warm-up - slow walking, -stretching exercises (scapular muscles, pelvic flexors, hamstrings, and gastrocnemius) -body rotation (body rotation pattern)	3/wk., 60 minutes	Parkinson Fatigue Scale (PFS) Modified Fatigue Impact Scale (MFIS) Functional Independence Measure (FIM)	Fatigue and ADL improved interventional group

Statistical analysis and results: -

The RCTs show a total of 245 participants in all been studied. The age group involved was above 20 years, the stage was 0- 4 on Hoehn and Yar scale, disease duration studied was from 1 year to 18 years. The common fatigue scale was the fatigue severity scale with a score of 4 at baseline. (Table: - 1).

With PEDro analysis all the 5 studies had eligibility criteria mentioned, all the studies were randomly allocated, except one study 4 studies performed concealed allocation, all the studies

had groups similar at baseline, none of the 5 studies did a subject blinding, 3 out 5 studies performed therapist and assessor blinding, only 2 studies showed at least one key Outcome from 85% subjects, only 1 study mentioned intention to treat, between-group statistical comparisons were done in all the studies, none had point measures and measures of variability. The average score on the PEDro scale was 5.8 only out of 10 which shows average evidence interventions on fatigue.

In Table:2 out of 5 RCT studies, only 2 studies had three groups for comparison. Common exercise types used were cardiovascular, strengthening, and vestibular rehabilitation. The common outcome measure used was physical activity scale, quality of life,endurance test, 1 RM, fatigue scale. An average of 30 to 45 minutes of treatment duration has been considered. Most of the treatment parameters followed the ACSM guideline proposed for Parkinson's Disease. Out of 5 systematically analysedstudies, only 3 showed improvement in fatigue which does not rule out the fact that exercise benefits the population having fatigue-related Parkinson's Disease.

Discussion: -

With very scant randomized controlled trialson fatigue as their outcome measure, which is discussed in this study, there is a considerable need to do more RCTs. Few other non-randomized studies which included dance, acupuncture, Nordic walking, cognitive behavioural therapy, comparing treadmill with strengthening exercises, fatigue management program was not included in the study as dint meet PEDro criteria.

The occurrence of fatigue is mostly reported in the early stage of the disease is seen to be worsening with disease severity and comorbidities. In these studies, no exercises have been reproduced to find their efficacy. With different interventions compared, the study is unable to strongly suggest any particular protocol to follow.

Studies have not shown any objective measurement with biomarkers that can measure the levels of physiological fatigue and compare it with the perceived fatigue. There have been studies using Functional magnetic resonance, Electromyography, Blood biomarkers, Cerebrospinal fluid markers for analysing the pathways activated and inflammatory levels. These outcome measures are mostly not reproducible due to ethical issues or either put the participants go through pain and fear of needles.

Salivary, Urine fluids can be used for measuring fatigue levels, these tests can also be suggested while undergoing therapy sessions at the clinical levels. Such outcomes are very useful in planning and altering the protocol for patients with Fatigue-related Parkinson's Disease.

An exercise which used vestibular rehabilitation was proved to cost-effective, safe and easily applied in clinics and home with minimal facilities. More such resource-poor and resource-rich exercise protocols covering the rural and urban population in India should be standardized so that the disease progression and severity of the disease can be reduced, the results can be generalized. Even though there is variation in Parkinson's Disease, such varied symptoms can be controlled in the clinical setup or community level with an entire focus on the common complaint reported as fatigue. Kostic VS et al 2016 in their study have insisted on the need for an evidence-based guideline or clinically established approach for the treatment of fatigue in Parkinson's Disease.

S. Coe et al 2018 showed significant improvement in sleep and changes in sedentary activities, but they failed to show any improvement in self-reported fatigue among the patients. It supports this in a way emphasizing the need for measurable non-invasive biomarkers. As self-reported fatigue may provide variation in results that were inefficient to be generalized. They in their study insisted on investigating the role of behavioural intervention in non-motor symptoms.

A study done by Lamotte, G et al in 2015 expressed the need for a more common-sense approach that varies with the approach of the clinical therapist, the findings are in contrast to this systematic study. Brown R.G et al 2005 have shown to provide counselling on fatigue being an independent symptom occurring and not as a reflection of other non-motor symptoms, which supports this study analysis on physiotherapy intervention aiming at fatigue. Cochrane G. S. et al in 2015 have contrasted the results of the previous study that all the non-motor symptoms cannot be treated, although exercise has also not shown significant improvement in fatigue levels, patients have reported being energetic post-exercise session.

Friedman, J et al 2016 have suggested current research to be focused on the identification of biological markers and correlates of fatigue that may provide insights into the development of effective treatments, which supports this study that since 2016 suggestions have been provided but no studies have claimed to have addressed the research gap yet. Even if biomarkers and imaging studies are done, they are costly and can be reproduced only in a laboratory setting.

Petzinger, G.M. et al supported in their study that the type of exercise affects the brain circuitry but with skilled exercise affecting frontal-striatal related circuits, then pure aerobic exercise. This study has contrasted with this systematic analysis for showing interventions with more on aerobic exercise as Nordic walking, treadmill, cycle ergometry, etc. Hence the need to analyse the effect of multi-modal type of exercise that is feasible in clinical and community-based set-up.

Amirabas et al 2020 thought in their study the objective was not to analyse the fatigue but still the MFIS score showed significant improvement. Their study provided theoretical insight into the probable role of neuroplasticity as the beneficial effects. They also suggest the connection between vestibular training and improvement in fatigue.

A home-based treadmill walking appeared to be feasible and a pragmatic form of training for Parkinson's Disease canning et al 2012 suggested further investigations to be done for administering more safer dose while progressing intensity and duration, hence it supports this systematic review for the need for standardization.But the study done by Winward et al 2011 was in contrast to the above study showing no improvement in fatigue outcome with 12 weeks of gym-based exercises because the frequency of exercise completed in the gym-based trial would have been insufficient to reduced fatigue, which emphasizes the fact that parameters for exercises should be established.

A study involving 20 patients with Parkinson's Disease who were subjected to Nordic walking for 12 weeks showed improvement in fatigue, the intensity, and type of training had to be tailored to the needs and possibilities of Idiopathic Parkinson's Disease. Cugusi et al 2015 believed the activity not regulated with specific guidelines may fail to achieve real and beneficial effects.

None of the articles included in the study have used a physiological non-invasive biomarker to assess the pre and post fatigue levels.

Limitations of these studies are even though they were studies available for fatigue, these studies were not included as theydid not meet the RCT criteria, some were not physiotherapy interventions. This made the study narrow down with less number to compare.

Conclusion: -

This systematic review has reported the available studies for fatigue which were measured with scales as an objective assessment for diagnosis and prognostic tool. There is a clear need for further research which is directed towards randomization, optimizing the exercise protocol in terms of intensity, frequency, and duration with the available exercise strategies proposed rather than finding new interventions. Hence a multi-dimensional exercise protocol with the most feasible exercises is to be framed, whose efficacy on fatigue to be measured with appropriate physiological non-invasive biomarkers are strongly insisted. Such studies shall give an insight for the therapists to tailor-make the intervention under a therapeutic framework. This therapeutic framework shall suggest the therapists globally on the intensity,duration, repetition, choice of exercise.

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