

Non-Pharmacological Therapy to Improving the Health Related Quality of Life in Patients Suffering with Chronic Fatigue Syndrome: A Systematic Review

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Abstract

Background

Chronic fatigue syndrome (CFS) is defined by excessive exhaustion that lasts for at least 6 months and that is not properly understood by an underlying medical condition (Reeves et al., 2007). Physical or mental exertion makes the tiredness worse. Sufficient resting periods do not make it better. There are several ideas about the origin of chronic fatigue syndrome, varying from viral infections to psychological stress. Some medical professionals think a number of variables may contribute to the development of chronic fatigue syndrome. Age and Sex are the two mentionable factors that may contribute to the elevated risk of CFS. Exercise based rehabilitation, Massage therapy, Electrical stimulation are some of the mentionable physical therapies that are used for the management of the condition.

Aim

To understand the role of physical therapy in improving the quality of life in patients suffering from chronic fatigue syndrome due to COVID 19 and cancer chemotherapy

Data sources

The various references articles were collected from five distinct databases which included Medline, PubMed, Cochrane, Embase, and Scopus.

Study selection

Only RCT were considered for the study. The various research papers, abstracts and any other presentations were excluded.

Data extraction

Descriptive information about the number of patients, therapy and outcomes were extracted from the papers

Data synthesis

A final of 40 RCT's were included for the review paper. Of the various RCT for cancer and COVID related fatigue reduction exercise was found to have beneficial effects in most of the studies. Massage therapy also showed significant improvement in patients. However, transeletrical nerve stimulation there was not much difference between control and intervention groups. Though many of the trials showed favorable outcomes for exercise and massage some of the trials contradicted the observation.

Limitations

In this review only cancer and COVID-19 related fatigue could be considered. The fatigue due to Dengue or any other viral disease though existent there are no recorded trials. Thus this study is exclusively limited to two of major diseases only.

Conclusion

This review highlights the fact that physical therapy in fact has a positive effect on reducing fatigue. However, not all forms of physical therapy are successful for this. Further research and trials are needed to see if physical therapy other than exercise and message could be helpful in controlling the fatigue.

Keywords: Physical therapy, Exercise, electrical stimulation, chronic fatigue, COVID-19, Chemotherapy, massage therapy, quality of life

I. INTRODUCTION

Cancer-related fatigue (CRF) is a common and upsetting side effect of cancer and cancer therapies, particularly when rest and sleep alone are insufficient to resolve the issue. After a cancer diagnosis and treatment, fatigue caused might last for months or even years (Berger et al., 2012). People who have CRF say they feel exhausted, frail, sluggish, and devoid of vitality. The symptoms of CRF are reported by nearly all cancer patients who are undergoing treatment, which may include surgery, radiation therapy, chemotherapy, and immunotherapy. The effects of this persistent tiredness on the body, mind, and emotions may be quite disruptive. In regards to COVID-19, it has been noted that with symptoms generally associated with "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome" (ME/CFS), a sizable number of COVID-19 patients are experiencing prolonged "Post-COVID-19 Fatigue Syndrome" (Wostyn, 2021). However, no definitive pathophysiological justification has yet been offered. Originally known as "Myalgic Encephalomyelitis" (ME), "Post-Viral Fatigue Syndrome" (PVFS) is basically the same illness as

“Myalgic Encephalomyelitis / Chronic Fatigue Syndrome” (ME/CFS). The clinical (diagnostic) evaluations for PVFS and ME/CFS are identical, and the “World Health Organization” classifies both conditions as neurological illnesses. A diagnosis of ME/CFS must be made based on “chronic fatigue” lasting six months or more without a plausible cause. As COVID-19 is still a comparatively new and complicated illness with many outcomes, longitudinal studies following the symptoms of post-COVID-19 patients over a period of six months or more are just now becoming available. The course of therapy will depend on the symptoms. Making modifications to one's lifestyle and receiving an early diagnosis can all be helpful. In the management of the symptoms associated with CFS, physical therapy can be advantageous. The patient and the physical therapist will collaborate to create a treatment plan for unique problems. Discomfort reduction, and enhancing the capacity to carry out everyday tasks is the major goal in this process. The goal of treatment for CFS patients is to increase their short-term stamina and strength due to their chronic exhaustion, discomfort, and weakness (Marques et al., 2015). Among the possible physical therapy remedies, physical therapists could create a program to assist in conserving energy while performing regular tasks. Exercises that include movement and strength are vital to overcome fatigue. Moving around might also help the patient feel less discomfort. Manual treatment to assist relieve the issues, the physical therapist could employ manual (hands-on) treatment. Skin, bones, and soft tissues are moved during this procedure to aid with pain relief and improved mobility. Considering the above mentioned aspects associated with CFS and related plausible treatments, in the current study, review of studies of Randomized Controlled Trials [RCT] associated with the effect of physical therapy in improving the quality of life in patients suffering with CFS would be the focus of the study. It is worth mentioning in this regard that the major aspect of the RCT is segregation of participants into two groups at random, with one getting the intervention under study (the “experimental group”) and the other (“the comparison group or control group”) receiving a different (traditional) therapy. Thus, in the current study, the studies focusing on the effect of physical therapy in improving the quality of life in patients suffering with CFS, which are based on the analysis of the experiment and the control group would be considered in the current study. It would be useful in effectively understanding and determining the impact of physical therapy on patients with CFS.

II. RESEARCH OBJECTIVES

1. To understand the effect of physical therapy in improving the quality of life in chemotherapy patients
2. To understand the effect of physical therapy in improving the quality of life in patients who are recovering from COVID-19 infection

Methods

a. Data sources and searches

The databases searched were Medline, PubMed, Cochrane, Embase, and Scopus. Exercise, Chemotherapy, Chronic Fatigue, COVID-19, Physical Therapy, and Dengue were some of the search terms used. However using just one keyword produced too many search results, therefore search terms were utilised. The different databases employed search strings that were created using Boolean operators. There are several search terms that were used, including "exercise and quality of life in cancer chemotherapy patients," "electrical stimulation and quality of life in cancer chemotherapy patients," "massage and quality of life in cancer chemotherapy patients," "exercise and Covid 19 fatigue," "electrical stimulation and Covid 19 fatigue," and "exercise and improvement in quality of life post Covid" (used for searching cochrane). Articles collected from Medline / Pubmed ranged from 705 (2001-2022) to 75 (using search term 6), 1923 (using various search keywords from 1-6) to 2488 (using various search terms from 1–5) in Cochrane, and 2488 (using various search terms from 1–5) in Embase.

b. Study selection

4030 of the 6191 papers that were used for screening were disqualified since they were research articles and not RCTs. Therefore, only 2161 papers were reviewed further. 700 of the 2161 publications that were reviewed were removed because they lacked RCTs. 30 of the 1461 remaining articles were not retrievable. Thus, 1431 items in all were taken into account for the assessment. 1290 publications were not highly relevant to the study, while 100 articles were continuing RCTs. Only 40 papers were included as a result of the final evaluation based on the study's objectives and queries. For the review, a total of 40 papers were included. The PRISMA sheet summarizing the same is presented in Fig.1

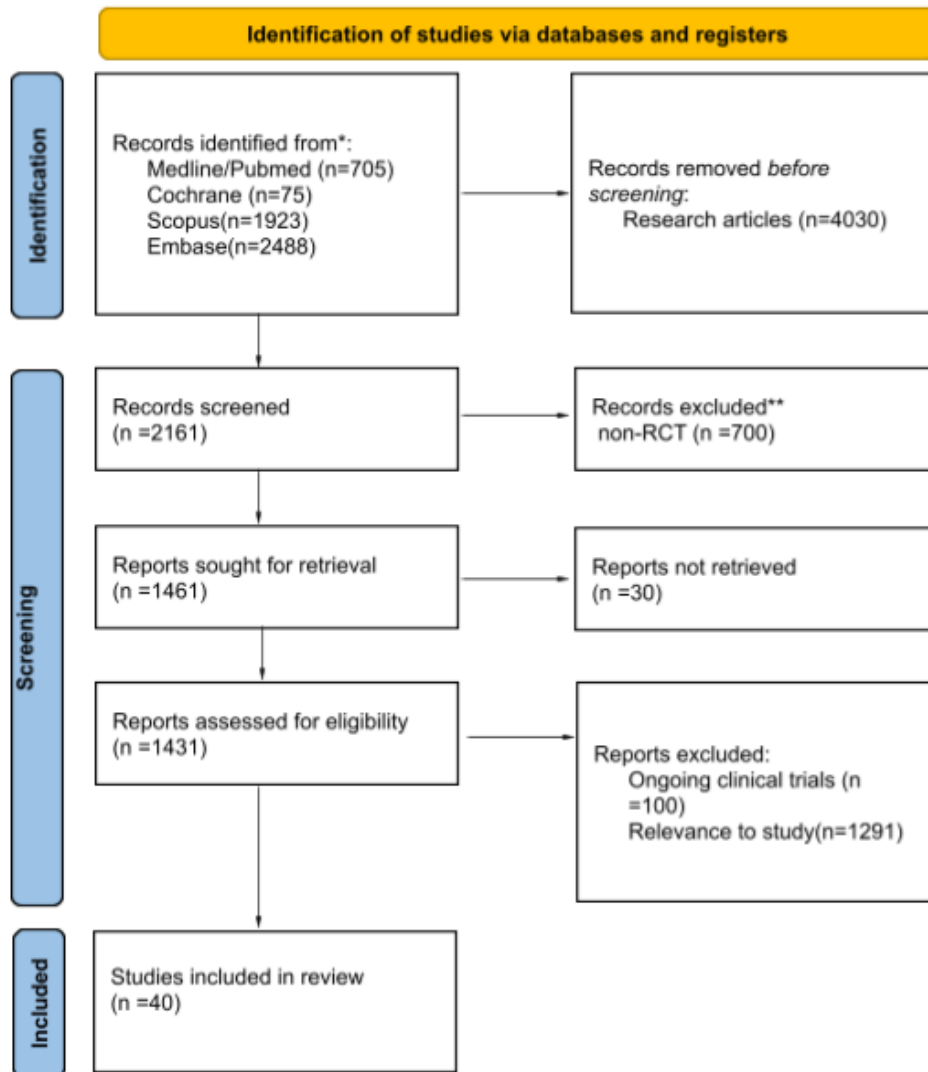


Fig 1: PRISMA summarizing the final selection of studies

c. Data extraction and quality assessment

The data from the various RCT was extracted independently by two reviewers. The initial filtering of the various studies and selection of RCT was overviewed by two reviewers. The final RCT selection was overviewed by the same two reviewers. Risk of bias assessment was done using the Cochrane handbook for RCT. Any discrepancy between the reviewers was sorted out by mutual discussion such that a consensus was reached.

d. Data synthesis and analysis

The various interventions from RCT were evaluated. The outcomes from the studies were also evaluated. Based on the intervention and outcomes the review was developed

III. RESULTS

a. Trial inclusion for chemotherapy and characteristics

Samuel et al. (2019) and Lin et al. (2021) conducted a study of patients with head and neck cancer undergoing CRT [chemo-radiotherapy]. Lu et al. (2019) and Khiewkhern et al. (2013), in their study and associated trial included patients undergoing chemotherapy-treated colorectal cancer. Similarly, Dhawan et al. (2020), conducted a trial consisting of cancer patients who were receiving chemotherapeutic drugs “paclitaxel and carboplatin” and they were suffering from “Chemotherapy-induced peripheral neuropathy” (CIPN). Yong An et al. (2020), conducted an RCT consisting of patients of breast cancer, for whom chemotherapy was being initiated. Similar such study was carried out by Bland et al. (2019) and Dong et al. (2019), and Koevoets et al. (2022), as well. The study group in Dong et al. (2019), were women within the age group of 42-60 years who had been operated on for breast cancer. Kirkham et al. (2019), in their trial included 73 early-stage breast cancer patients who were scheduled to receive adjuvant chemotherapy. Song et al., performed a trial on breast cancer patients who were diagnosed with CIPN followed by

chemotherapy. Similar such trials have been reported by Eyigör et al. (2021), Mostafaei et al.(2021), , Izgu et al. (2019), , Wei et al. (2022), and Kinkead et al. (2018), wherein, patients with breast cancer, breast cancer patients who were receiving chemotherapy, breast cancer patients receiving “adjuvant paclitaxel” and survivors of breast cancer were considered in the studies. In the study conducted by Strandberg et al. (2022), a total of 2051 patients who were newly diagnosed with colorectal, prostate, or breast cancer were included in the trial. Zimmer et al. (2018), performed a trial consisting of patients (stage IV), who were undergoing outpatient palliative treatment including a median of 23.5 chemotherapy cycles of different regimens. Adults aged 28-69 years, who were newly diagnosed with acute leukemia were considered for the trial in the study conducted by Bryant et al. The study conducted by Hu et al., composed of patients undergoing chemotherapy of “nasopharyngeal carcinoma” (NPC). Müller et al. (2021), had patients who were undergoing neurotoxic chemotherapy. Patients who were suffering from gastrointestinal cancer and undergoing chemotherapy were considered for the trial in the study conducted by Hong et al. In the study conducted by Stuecher et al. (2019), the trial consisted of patients with “gastrointestinal cancer (GIC)”, .However, in the study; patients in the advanced stage of the condition undergoing first line chemotherapy were considered for the trial. The focus of the trial by Guo et al., was also patients with “advanced gastric cancer (AGC)”, who were experiencing CINV. Quist et al. (2020), included patients with advanced inoperable lung cancer. The focus of the study conducted by Ikio et al. (2022), was 42 patients with “chemotherapy-induced peripheral neuropathy (CIPN)”. Childs et al., conducted a similar study which focussed on CIPN. 30 cancer patients undergoing “taxane-based chemotherapy” were included in the trial of the study conducted by Saraboon & Siriphorn (2021) Dikmen & Terzioglu (2019), included patients who had gynecologic cancer and were undergoing chemotherapy. Patients with advanced cancer and “CRF scores of $\geq 4/10$ on the Edmonton Symptom Assessment Scale” were considered in the trial of the study conducted by Yennurajalingam et al. (2021) Patients with primary or metastatic liver cancer were considered for the trial in the study conducted by Xie et al. (2017). In the study conducted by Adamsen et al. (2009), patients with cancer within the age range of 20-65 were considered for the trial in the study.

Apart from sample being one of the major aspects of trials included in the considered studies, the invention used on the samples is also an integral aspect. On analyzing the characteristics of the trials from the perspective of the inventions being used, it can be noted that, in the majority of the considered studies (n=25), some form of exercise has been included as the intervention implemented in the trial of the study. In 3 of the considered studies in this review (n=3), electrical stimulation has been used as the intervention in the trial, whereas in one of those three studies Childs et al. (2021), “transcutaneous electrical nerve stimulation” has been compared with Scrambler Therapy. In another 2 of the considered studies in this review, message has been used as the intervention in the trial, one of these studies used classical massage as the intervention and in the other study Swedish massage therapy (SMT) has been used as the intervention in the trial. In the study conducted by Kinkead et al. (2018) which used SMT as the intervention, active control condition (light touch [LT]) and waitlist control (WLC) has been compared with SMT in terms of the efficaciousness. In one of the considered study for review Eyigör et al. (2021), hatha yoga has been considered as an intervention.

b. Trial inclusion for COVID-19 and characteristics

In regards to the participants recruited in the trial of the study conducted by Nambi et al. (2022) community-dwelling older men [age range of 60-80 years] with post-COVID-19 sarcopenia symptoms were considered for the study. Okan et al., in their study, they considered post-Covid-19 dyspneic individuals. The study conducted by Badran et al.(2022), included individuals who were previously positive for COVID-19 in the trial. Almazán et al. (2022), in their trial included individuals with post-COVID-19 conditions who were suffering from chronic symptomatic phase that were lasting for more than 12 weeks. Sevilla et al. (2021), considered university employees for their trial.

In regards to the intervention used in the above discussed studies [n=6], it has been noted that five of the studies considered some form of exercise as the intervention in the trial for the management of the condition. In the study conducted by Badran et al. (2022), “Transcutaneous auricular vagus nerve stimulation (taVNS)” has been considered as the intervention. While in the study conducted by Sevilla et al. (2021) “lifestyle exercise and nutrition intervention” has been considered for the trial. In the study conducted by Okan et al. (2022) breathing exercises have been considered as the intervention for the trial.

d. Intervention effects of different physical therapy approaches and their outcomes

Exercise based rehabilitation and outcome

Among all the studies considered for reviewing to understand the impact of physical therapy on chemotherapy induced CFS, [n=25] of the studies have used exercise in some form as the intervention in these trials. In all the studies it has been reported that the use of exercise as a form of intervention in the trial when analyzed and compared to patients who were randomly assigned to receive usual care, the intervention group showed a much lower level of anxiety and despair as well as a significantly higher level of muscular strength. It has also been reported in some of these trials that the implementation of exercise as a means of intervention not only helps in enhancing the QoL, but also helps in maintaining VO₂peak, strength Kirkham et al. (2019). However, the mentioned finding contradicts the study conducted by Quist et al. (2020) wherein it has been reported that the use of exercise as an intervention did not help in enhancing VO₂ peak. The use of indoor exercise, Baduanjin exercise, has been reported to have significant positive impact on the management and reduction of fatigue. The use of resistance exercise has been observed to be not just beneficial in the management of physical fatigue but also in the management of mental fatigue.

Massage therapy and outcomes

On analyzing the impact of use of massage therapy as an intervention in CFS, it has been noted that in the studies where massage was implemented as an intervention, its effects on reducing “chemotherapy-induced peripheral neuropathic pain” and improving quality of life were shown to be

favorable. In the study conducted by Izgu et al. (2019), it has been noted that with the implementation of classical massage, the QOL score's sensory and motor sub-scale values indicated statistically significant changes over time in favor of the CMG ($p < 0.05$). At week 12, the CMG considerably outperformed the CG in terms of the “sensory action potential amplitude of the median nerve and the tibial nerve delay”. In this regard, it has also been noted that SMT, as the form of intervention in the experiment, showed clinically meaningful outcomes by demonstrating SMT's intervention's considerable efficacy in reducing CRF. Analysis of the effects of a gentle “aromatherapy-infused Thai massage” has been done. The study's conclusions showed that Thai massage with mild aromatherapy benefits cancer patients getting chemotherapy by boosting lymphocytes, which is helpful for their immune systems. It may help reduce the severity of recurring symptoms as per the study conducted by Khiewkhern et al. (2013).

In regards to the management of CFS cause as an after-effect of Covid-19, all studies that included exercise in some way as the intervention in the trials for the study [n=5] stated that the applied intervention had a favorable effect on the study samples. When compared to the control group, exercises like breathing exercises have been shown to significantly reduce tiredness, dyspnea, perceived effort, and physical condition. However, the breathing exercise group showed the greatest improvements in these areas and in aerobic capacity. In the study conducted by Okan et al. (2022) it has been reported that in the intervention group, the posttest FEV1, FVC, and MVV values were considerably higher than the pretest values ($p < 0.001$), while no significant changes were identified in the control group. In the intervention group, the six-minute walk distance rose by 54.27 m, compared to 4.69 m in the control group. Improvements in pulmonary functions, quality of life, and activity capacity were seen in dyspneic post-Covid-19 patients when breathing exercise training was performed via telemedicine.

Electrical stimulation and outcome

In regards to the use of electrical stimulation as an intervention in the management of CFS induced by chemotherapy, it has been noted that only one of the study considered for the review reported positive impact of NES in terms of lowering the intensity of vomiting and nausea as well as improving appetite. It has been further reported in this regard that after treatment, NES showed stronger efficacy than sham NES in lowering the intensity of nausea ($P = 0.02$), vomiting ($P = 0.04$), as well as improving appetite ($P = 0.02$). Additionally, no adverse reactions to NES therapy were found.

In context to the use of “electoral stimulation in the management” of CFS caused by Covid-19, it has been reported that it is possible and safe to self-administer taVNS as the intervention in the experiment. Data trends suggest that taVNS may modestly to moderately lessen the symptoms of mental fatigue in a segment of patients. In the study four weeks of at-home self-administered taVNS was implemented.

Self-Reported and objectively measured chemotherapy and characteristics

In regards to the measurement of the impact of the interventions used in the study trials considered for the current review, it has been observed that the majority of the studies considered for understanding CFS induced by chemotherapy, considered objectively measuring the impact of the interventions [n=30]. In one of the studies associated with CFS induced by chemotherapy considered for this review, an integrated objective and subjective approach for measuring the impact of the intervention has been used. While in only one of the studies associated with CFS induced by chemotherapy, a subjectively approach has been considered for the measurement of the impact of the used intervention in the trial, wherein the focus has been on patient-reported outcomes.

Self-Reported and objectively measured Covid-19 and characteristics

In regards to the studies considered for analyzing the impact of physical therapy on CFS caused by Covid-19, it has been noted that all the studies [n=6] used objective measurement for assessing the impact of the interventions used in the trials. In the study conducted by Okan et al. (2022) “six-minute-walk-tests, Pulmonary function tests, and St George's Respiratory Questionnaire”, have been used as the means of objectively measuring the impact of the implemented intervention in the trial. In the study conducted by Blanco et al. (2022) “multidimensional dyspnoea-12 questionnaire and Borg Scale” has been used to objectively measure the impact of the implemented intervention in the trial conducted in the study. Handgrip strength, kinesiophobia level, quality of life has been used to evaluate the impact of the implemented intervention in the study conducted by (Nambi et al., 2022). In the study conducted by Almazán et al. (2022) cardiovascular and strength markers has been used as the means to objectively measure the impact of the implemented intervention in the trial. “Health Promoting Lifestyle Profile II questionnaire” has been used as the tool for objectively measuring the impact of the used intervention in the study conducted by Sevilla et al. (2021). In the study conducted by Badran et al. (2022) the used taVNS system was self-administrative in nature, which was also used for remote monitoring physiological biomarkers based on which, the impact of the used intervention in the trial has been determined.

Tables summarizing the study characteristics of the identified studies

Year	Author	Nature of the study	Number of patients	Type of intervention	Study duration	Outcome
2009	Lis Adamsen, Morten Quist, Christina	RCT	269 patients	Supervised exercise using high intensity	six weeks	The intervention used in the study was noted to reduce fatigue and

	Andersen, Tom Møller, Jørn Herrstedt, Dorte Kronborg, Marie T Baadsgaard, Kirsten Vistisen, Julie Midtgaard, Birgitte Christiansen, Maria Stage, Morten T Kronborg, Mikael Rørth			cardiovascular and resistance training, training, massage, relaxation and body awareness compared with conventional care.		improved aerobic capacity, vitality, muscular strength, aerobic capacity, and emotional wellbeing, functional and physical, however, the quality of life did not improve.
2020	Ki-Yong An, Andria R Morielli, Dong-Woo Kang , Christine M Friedenreich , Donald C McKenzie , Karen Gelmon, John R Mackey, Robert D Reid , Kerry S Courneya	multicenter trial	301	Combined Aerobic and Resistance Exercise (CARE) Trial has been compared different types and doses of exercise	24 months	The study revealed that the used intervention in the study during and after breast cancer chemotherapy contributes in enhancing longer-term patient-reported outcomes along with health-related fitness when compared to individually performing aerobic exercise.
2022	Bashar W Badran , Sarah M Huffman , Morgan Dancy , Christopher W Austelle 1, Marom Bikson , Steven A Kautz , Mark S George	pilot randomized controlled trial	13	Transcutaneous auricular vagus nerve stimulation	four weeks	The trends in the data collected through the study revealed that taVNS may have mild to moderate in minimizing mental fatigue symptoms when treating long COVID" symptom. The study also demonstrates that taVNS is a safe and feasible self-administered intervention.
2012	Ann M Berger , Lynn H Gerber, Deborah K Mayer	Review of knowledge (Systematic literature review)	N.A.	nonpharmacologic and pharmacologic interventions	N.A.	Based on the reviewed literatures, the researchers opined that psychosocial and Physical interventions are recommended are advised for cancer-related fatigue
2019	Kelcey A Bland, Amy A Kirkham 2, Joshua Bovard, Tamara Shenkier, David Zucker, Donald C McKenzie, Margot K Davis, Karen A Gelmon,	RCT	27	immediate exercise, delayed exercise, Supervised aerobic, balance and resistance training	8-12 weeks	global health status / quality of life was recorded to be higher among the group who were provided with immediate exercise during taxane chemotherapy as compared to the group who were provided with

	Kristin L Campbell					delayed exercise. However, in case of both the groups, worse CIPN20 sensory and motor symptom scores were observed. The finding revealed that exercise may reduce CIPN during taxane chemotherapy and may improve taxane adherence among women with breast cancer.
2021	Daniel S Childs, Jennifer G Le-Rademacher, Ryan McMurray, Markus Bendel, Carrie O'Neill, Thomas J Smith, Charles L Loprinzi	cross over trial	Fifty patients	Scrambler therapy vs. transcutaneous electrical nerve stimulation (TENS)	2-week treatment period and 8-week observation period	The study noticed a 50% or more reduction in primary symptom (pain or tingling) on the last day of the treatment of Scrambler-treated patients, which has been recorded among 60% of the patients, while for the group comprising of TENS-treated patients the reduction has been recorded in only among 25% of the patients.
2020	Shelly Dhawan, Rachel Andrews, Lalit Kumar, Sanjay Wadhwa, Garima Shukla	RCT	45 cancer patients	home-based muscle strengthening and balancing exercise	10 weeks	As compared to the usual-care group, among the exercise group major reduction in neuropathic pain scores, improvement in Functional QOL, Symptom QOL and Symptom QOL scores were observed were observed in the study.
2019	Hacer Alan Dikmen, Fusun Terzioglu	RCT	Eighty participants	reflexology and progressive muscle relaxation	during chemotherapy of patients	Significant reduction in pain severity and fatigue along with increase in QoL was observed among the group who were provided reflexology and reflexology + PMR groups. In the group where PMR alone was provided, significant reduction in pain severity and fatigue was observed but no change in QoL was noted.
2019	Xiaosheng Dong, Xiangren Yi, Dezong Gao, Zan Gao, Shuyuan	RCT	Sixty participants	combined exercise intervention based on internet and social media	12 weeks	The findings of the study revealed that CEIBISMS contributes to significant improvement in arm

	Huang, Mengyao Chao, Wenxin Chen, Meng Ding			software (CEIBISMS)		lifting test, stand-up and sit-down chair test. It offers rehabilitative effects in QoL and muscle strength of postoperative patients with breast cancer
2021	Sibel Eyigör, Sebnem Apaydin, Hilal Yesil 3, Goksel Tanigor, Derya Hopanci Bicakli	Rando- mized, Single- Blind, Control led Trial	Thirty- one patients	yoga	10 weeks	Among the group who under yoga significant improvements in the post treatment EORTC QLQ functional and global scores was noted. Yoga has been concluded to have beneficial impact on QoLin patients with breast cancer.
2021	Guillermo García Pérez de Sevilla, Olga Barceló Guido, María de la Paz De la Cruz, Ascensión Blanco Fernández, Lidia B Alejo, María Montero Martínez, Margarita Pérez- Ruiz	RCT	Twenty- three	lifestyle intervention	18 weeks	Lifestyle among the intervention group has been noted to improve significantly, particularly in the categories of Physical Activity, Health Responsibility, and Nutrition. Improvement in health-related quality of life has also been observed.
2018	Wen-Cheng Guo, Fang Wang	RCT	One hundred twenty- four	nerve electrical stimulation	During the treatment of chemotherap y among patients with advanced gastric cancer	Followed by the treatment, the intervention demonstrated effectiveness in reducing the severity of nausea, vomiting and vomiting.
2022	Yuta Ikio , Akira Sagari, Akira Nakashima, Daiki Matsuda 2, Terumitsu Sawai, Toshio Higashi	pilot random ized controll ed trial	42	combined hand exercise intervention	At baseline (T0) and after one (T1) and two (T2) chemotherap y cycles.	When compared to the control group at T2, the intervention group's decline in MHQ's activities of daily living was significantly suppressed in the intention-to-treat analysis. When compared to the control group at T2, the intervention group's decline in activities of daily living was significantly suppressed in the as-treated analysis. At T2, pain in the intervention group was significantly reduced compared to that in the

						control group. The researchers opined that combined hand exercise intervention may enhance upper-extremity function.
2019	Nur Izgu, Zehra Gok Metin, Canan Karadas, Leyla Ozdemir, Nil Çetin, Umut Demirci	assessor-blinded randomized controlled trial	40	classical massage group	16 weeks	The findings of the study suggests that classical massage is effective in preventing chemotherapy-induced peripheral neuropathic pain and also enhances QOL and has beneficial impact on NCS .
2022	Amaya Jimeno-Almazán 1 2, Francisco Franco-López 2, Ángel Buendía-Romero 2, Alejandro Martínez-Cava 2, José Antonio Sánchez-Agar, Bernardino J Sánchez-Alcaraz Martínez, Javier Courel-Ibáñez, Jesús G Pallarés	RCT	39 participants	supervised therapeutic exercise intervention	8 weeks	The study reveals that as compared to WHO recommendation, “a tailored, supervised concurrent training at low and moderate intensity for both resistance and endurance training” is safer, effective and well-tolerated intervention in conditions associated with post-Covid 19.
2013	Santisith Khiewkhern, Supanee Promthet, Aemkhea Sukprasert, Wichai Eunhpinitpong, Peter Bradshaw	single-blind, randomized-controlled trial	Sixty-six	aromatherapy with light Thai massage	1-week period	In the treatment group, significantly higher mean lymphocyte count was observed at pre-assessment values . The findings of the study reveals that aromatherapy with light Thai massage can be useful for immune systems of cancer patients who are undergoing chemotherapy.
2018	Becky Kinkead, Pamela J Schettler, Erika R Larson, Dedric Carroll, Margaret Sharenko, James Nettles, Sherry A Edwards, Andrew H Miller, Mylin A Torres, Boadie W Dunlop, Jeffrey J Rakofsky, Mark Hyman Rapaport	early phase, randomized, single-masked , 6-week investigation	66	Swedish massage therapy (SMT) , active control condition (light touch [LT]) and waitlist control (WLC)	6-weeks	The findings of the study established that SMT provides clinically significant relief of CRF.

2019	Amy A Kirkham, Kelcey A Bland, Holly Wollmann, Alis Bonsignore, Don C McKenzie, Cheri Van Patten, Karen A Gelmon, Kristin Campbell	Clinical Trial	73 women	aerobic and resistance exercise	1-year	The findings revealed that evidence-based exercise programming which is provided with real-world implementation maintains QoL, strength, and VO ₂ peak at the time of adjuvant treatment.
2022	E. W. Koevoets, S. B. Schagen, M. B. de Ruiter, M. I. Geerlings, L. Witlox, E. van der Wall, M. M. Stuiver, G. S. Sonke, M. J. Velthuis, J. J. Jobsen, M. B. E. Menke-Pluijmers, E. Göker, C. C. van der Pol, M. E. M. M. Bos, L. W. Tick, N. A. van Holsteijn, J. van der Palen, A. M. May, E. M. Monninkhof, and PAM study group	RCT	181	aerobic and strength training, Nordic/power walking	6-month	The intervention enhanced self-reported physical fitness, cognitive functioning, QoL, fatigue, depression among breast cancer patients undergoing chemo with cognitive problems.
2021	Kuan-Yin Lin, Hui-Ching Cheng, Chia-Jui Yen, Ching-Hsia Hung, Yu-Ting Huang, Hsin-Lun Yang, Wan-Ting Cheng, Kun-Ling Tsai	pilot-randomized controlled trial	57	moderate-intensity combined aerobic, resistance and flexibility exercises	eight weeks	The study observed that combined aerobic, resistance and flexibility exercise program at the time of chemotherapy may contribute in enhancing physical fitness and HRQoL along with alleviating the deterioration of cardiovascular fitness among patients with HNC.
2019	Yun Lu, Hui-Qin Qu, Feng-Ying Chen, Xiao-Ting Li, Lan Cai, Shan Chen, Yuan-Yuan Sun	open-label, randomized controlled clinical trial	Ninety patients	Baduanjin qigong	24 weeks	The study revealed that Baduanjin qigong exercise can be effective in relieving CRF in patients with colorectal cancer who are undergoing chemotherapy and it can enhance physical activity level and sleep quality.
2015	M M Marques, V De Gucht, M J	systematic review	N.A.	behavioral interventions,	N.A	The interventions have been opined to have sustained

	Gouveia, I Leal, S Maes	and meta-analyses		graded physical activity		beneficial impacts on chronic fatigue management.
2021	Fatemeh Mostafaei, Mohammad Azizi, Amir Jalali, Nader Salari, and Parvin Abbasi	RCT	60	indoor exercise program	6 weeks	The mean fatigue intensity scores have been observed to be significantly reduced in the intervention group. The indoor exercise intervention was noted to reduce fatigue among women with breast cancer while undergoing chemo.
2021	Jana Müller, Markus Weiler, Andreas Schneeweis, Georg Martin Haag, Karen Steindorf, Wolfgang Wick, Joachim Wiskemann	RCT	170	sensorimotor-(SMT) and resistance training (RT)	6 months	The findings of the study demonstrated that SMT and/or RT contribute to alleviating subjectively perceived sensory CIPN symptoms.
2022	Gopal Nambi, Walid Kamal Abdelbasset, Saud M Alrawaili, Shereen H Elsayed, Anju Verma, Arul Vellaiyan, Marwa M Eid, Osama R Aldhafian, Naif Bin Nwihadh, Ayman K Saleh	RCT	76	low and high-intensity aerobic training, resistance training	8 weeks	Low intensity aerobic training exercises have been observed to be more effective in enhancing the clinical and psychological measures as compared to high-intensity aerobic training.
2022	Fatih Okan, Sevil Okan, Fadime Duran Yücesoy	RCT	52	breathing exercises given by telemedicine	5 weeks	The study observed improvements in pulmonary functions, QoL, and exercise capacities of dyspneic post-Covid-19 individuals on providing them breathing exercise training through telemedicine
2020	Morten Quist, Seppo W Langer, Christian Lillelund, Lærke Winther, Jørgen H Laursen, Karl B Christensen, Mikael Rørth, Lis Adamsen	RCT	218	supervised, structured exercise training program [exercise intervention]	12-week	Significant improvement in muscle strength along with social well-being observed among the patients. Reduction in the level of anxiety and depression along with increase in muscle strength has been

						observed among the intervention group.
2022	Cleofas Rodríguez-Blanco, Carlos Bernal-Utrera, Ernesto Anarte-Lazo, Manuel Saavedra-Hernandez, Elena De-La-Barrera-Aranda, Maria Angeles Serrera-Figallo, Maribel Gonzalez-Martin, Juan Jose Gonzalez-Gerez	Rando mized, controll ed, parallel , double-blinded , three-arm clinical trial	93 subjects	breathing exercises group, strength exercises group	14-days	significant improvements in perceived effort, dyspnoea, fatigue, physical state has been observed among breathing exercises group and strength exercises group
2019	Stephen Rajan Samuel, Arun G Maiya, Donald J Fernandes, Vasudeva Guddattu, P U Prakash Saxena, Jestina Rachel Kurian, Po-Ju Lin, Karen M Mustian	RCT	148 patients	exercise-based rehabilitation, structured exercise program of aerobic and active resistance exercises	11 weeks	Significant improvement in the functional capacity along with QoL and prevention of worsening of fatigue has been observed among the exercise group.
2021	Chanatsupang Saraboon, Akkradate Siriphorn	RCT	30	foam pad balance exercises	6 weeks	The findings of the study indicated that foam pad balance exercises at the time of chemotherapy can be implemented to reduce declining balance and improve physical performance and QoL of patients.
2020	Si-Yeon Song, Ji-Hye Park, Jin Sun Lee, Je Ryong Kim, Eun Hee Sohn, Mi Sook Jung, Hwa-Seung Yoo	single-center, random ized, placebo - controll ed trial	72 patients	low-frequency electrostimulation (ES)	14 days	In this study, no differences in NRS scores were noted among the patients of both the groups.
2021	Emelie Strandberg, Christopher Bean, Karianne Vassbakk-Svindland, Hannah L. Brooke, Katarina Sjövall, Sussanne Börjeson, Sveinung Berntsen, Karin	RCT	577	exercise intervention	6-months	The recruitment procedures used in comprehensive oncology exercise trials has been identified to need to emphasize to address barriers for participation among men, older patients patients and without university education. Individualized efforts are required to be made to enroll patients

	Nordin & Ingrid Demmelmaier					with low exercise self-efficacy and low outcome expectations of exercise.
2019	Katrin Stuecher, Claus Bolling, Lutz Vogt, Daniel Niederer, Katharina Schmidt, Axel Dignaß, Winfried Banzer	single-blind RCT	44	home-based moderate intensity exercise	before chemotherapy (T0), after two chemotherapy cycles (T1) and after 12 weeks	Results of the study indicated that home-based physical activity helps in enhancing postural sway and body composition and may contribute to stabilization of functional capacity in patients with advanced GIC at the time of chemotherapy.
2022	Xiaolin Wei, Ruzhen Yuan, Juan Yang, Wei Zheng, Yongmei Jin, Mingyue Wang, Jieting Jiang, Caiqin Wu, Kunpeng Li	pilot study	70 patients	Baduanjin exercise	3 months	The study revealed that Baduanjin exercise is associated with benefits related to subjective cognition and health-related quality of life among patients with breast cancer.
2021	Peter Wostyn	Review paper	N.A	cerebrospinal fluid drainage	N.A	Among patients with Covid-19, fatigue syndrome can be treated using cerebrospinal fluid drainage which may help in restoring glymphatic transport along with waste removal from the brain.
2017	Jing Xie, Lei-Hua Chen, Zhou-Yu Ning, Chen-Yue Zhang, Hao Chen, Zhen Chen, Zhi-Qiang Meng, Xiao-Yan Zhu	single-blind, randomized controlled trial	142	transcutaneous electrical acupoint stimulation	6 days	The findings of the study revealed that TEAS appears to be an effective and safe therapy for relieving gastrointestinal discomfort among cancer patients, followed by the chemotherapy.
2021	Sriram Yennurajalingam I, Vicente Valero, Zhanni Lu, Diane D Liu, Naifa L Busaidy, James M Reuben, Carolina Diaz Fleming, Janet L Williams, Kenneth R Hess, Karen Basen-Engquist, Eduardo Bruera	Phase II Randomized Double-Blind Controlled Trial	67 patients	physical activity (PA) and dexamethasone (Dex)	4 weeks	The study revealed that combination therapy of PA with Dex is feasible and contributes in improvement of CRF
2018	Philipp Zimmer, Sina Trebing, Ursula Timmers-	RCT	Thirty patients	supervised exercise program	2 weeks	The study demonstrated positive impacts of multimodal exercise

	Trebing, Alexander Schenk, Rainer Paust 5, Wilhelm Bloch, Roland Rudolph, Fiona Streckmann, Freerk T Baumann					program on CIPN, strength and balance on mCRC patients in a palliative setting
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IV. DISCUSSION

On analyzing the results of the studies considered for understanding the impact of physical therapy in CFS induced by chemotherapy, it has been observed that the studies that used massage as a form of intervention in the trial observed positive impact of the intervention on preventing chemotherapy-induced peripheral neuropathic pain and enhancing QoL (Izgu et al., 2019). It has been further observed in this regard that, SMT as the form of intervention in the trial demonstrated SMT that the intervention is significantly effective in relieving CRF, which demonstrated clinically significant results (Kinkead et al., 2018). In the study conducted by Khiewkhern et al. (2013) the impact of light Thai massage has been analyzed, which was integrated with aromatherapy. The findings of the study revealed that with light, “aromatherapy Thai massage” helps strengthen lymphocytes in cancer patients receiving chemotherapy, which is good for their immune systems. It can also lessen the intensity of frequent symptoms. In the study conducted by Xie et al. (2017) supervised exercise has been integrated by the researcher with awareness training and massage. The findings of the study revealed that the mentioned intervention in the trial is effective in minimizing fatigue along with enhancing physical and functional activity, muscular strength, aerobic capacity, and enhanced vitality and emotional wellbeing, however, no major impact was noted on the QoL of the participants of the trial. In the study conducted by Dikmen & Terzioglu (2019), where “reflexology and progressive muscle relaxation (PMR) exercises” have been used as the intervention in the trial, the findings of the study demonstrated that when it is given to patients of gynecologic cancer when they are undergoing chemotherapy, the intervention is effective in reducing fatigue and pain along with enhancing the QoL of the patients. Among all the studies considered for the review in regards to understanding the impact of physical therapies as an intervention for chemotherapy induced CFS, it has been noted that in majority of the studies [n=25] the used intervention of exercise in any form, yielded positive results in reducing fatigue, improving the QoL among the samples included in the trial along with reducing discomfort of chemotherapy noted few studies Xie et al. (2017). In addition to that, in one of the 25 studies, yoga has been used as the intervention in the trial wherein it has been noted that the intervention used in the trial is beneficial in improving the QoL among the patients, which has been noted to have significant effect on Phase angle (PA). In a considerable number of studies considered for the study [n=5], “aerobic and resistance exercise” has been used as the intervention in the trial. In all the five studies the implemented intervention has been observed to have a positive impact on the participants of the trials in terms of improving QoL and functional capacity of the respondents. It has also been noted in this context that the incorporation of “aerobic and resistance exercise” as the intervention helps in providing enhanced patient reported outcomes along with health associated fitness (An et al., 2020). In the studies in which resistance exercises have been specifically focused [n=2], the findings demonstrated that the intervention is effective in enhancing QoL, wherein it is beneficial in managing the symptoms, along with the physical function of the patients undergoing chemotherapy. It has been also noted in the study that in gastrointestinal cancer patients receiving chemotherapy, resistance exercise training decreased the likelihood of nausea and acid reflux, enhanced physical performance, and lessened tiredness and appetite loss. In regards to the use of electrical stimulation as the intervention in the trials, in only one of the three considered trials in this regard it has been reported that “nerve electrical stimulation (NES)” is effective in terms of reducing severity of vomiting, nausea, along with appetite improvement (Guo & Wang, 2018). However, in the study conducted by Song et al. (2020) and Childs et al. (2021) it has been noted that “low-frequency electro stimulation (ES)” device when compared to placebo, it is not significantly different and in alleviating CIPN symptoms Scrambler therapy has been noted to be better than TENS.

In regards to the studies considered for understanding the impact of physical intervention on CFS caused as an after-effect of Covid-19 [n=6], it has been noted that in all studies wherein exercise in some form has been considered as the intervention in the trials in the study [n=5], all the studies reported positive impact of the implemented intervention on the samples of the study. Exercises for instance breathing exercise have been reported to have significant positive impact on improvements in fatigue, dyspnea, perceived effort, and physical condition as compared to the control group, however the breathing exercise group had the highest advantages for dyspnea and aerobic capacity. On analyzing the impact of taVNS as the intervention in the trial it has been observed that it is possible and safe to self-administer taVNS. Trends in the data indicate that taVNS may reduce mental fatigue symptoms in a subgroup of people in a modest to moderate way. Furthermore, in regards to the use of aerobic training exercises as the intervention in the studies it has been observed that activities involving low-intensity aerobic training are more successful than exercises involving high-intensity aerobic training in enhancing “psychological (kinesiophobia and quality of life) and clinical (muscle strength) parameters” in post-COVID 19 Sarcopenia. The implementation of lifestyle exercise and nutrition intervention in the trial has demonstrated effectiveness in categories of Physical Activity, and Nutrition, Health Responsibility, wherein it has also been noted that in context to “health-related quality of life” (HrQoL) the used intervention provides with clinically significant results associated with improvement in the “Physical Component Summary”.

V. CONCLUSION

The review highlighted the fact that exercise and physical therapy are effective interventions in providing relief to fatigue patients. The overall quality of life was improved in these patients. However, the other kinds of therapy have not been very successful. More research is needed in order to establish the effects of these interventions as the review shows both favorable results and in some cases contradictory results as well.

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