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SYSTEMATIC REVIEW

Fatigue, post-exertional malaise and orthostatic intolerance: a map of Cochrane evidence relevant to rehabilitation for people with post COVID-19 condition

Chiara ARIENTI [1], Claudio CORDANI [2, 3] *, Stefano G. LAZZARINI [1], Matteo J. DEL FURIA [3], Stefano NEGRINI [2, 3], Carlotte KIEKENS [4]

[1]IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy; [2]Department of Biomedical, Surgical and Dental Sciences, University "La Statale", Milan, Italy; [3]IRCCS Istituto Ortopedico Galeazzi, Milan, Italy; [4]IRCCS MultiMedica, Milan, Italy

*Corresponding author: Claudio Cordani, Department of Biomedical, Surgical and Dental Sciences, University "La Statale", via della Commenda 10, 20122 Milan, Italy. E-mail: claudio.cordani@unimi.it

ABSTRACT

INTRODUCTION: Rehabilitation focuses on impairments, activity limitations and participation restrictions being informed by the underlying health condition. In the current absence of direct "evidence on" rehabilitation interventions for people with post-COVID-19 condition (PCC), we can search and synthesize the indirect "evidence relevant to" coming from interventions effective for the symptoms of PCC in other health conditions. The World Health Organization (WHO) required this information to inform expert teams and provide specific recommendations in their Guidelines. With this overview of reviews with mapping, we aimed to synthesize in a map the Cochrane evidence relevant to rehabilitation for fatigue, post-exertional malaise and orthostatic intolerance due to PCC.

EVIDENCE ACQUISITION: We searched the last five years' Cochrane Systematic Review (CSRs) using the terms "fatigue," "orthostatic intolerance," "rehabilitation" and their synonyms in the Cochrane Library. We extracted and summarized the available evidence using a map. We grouped the included CSRs for health conditions and interventions, indicating the effect and the quality of evidence.

EVIDENCE SYNTHESIS: Out of 1397 CSRs published between 2016 and 2021, we included 32 for fatigue and 4 for exercise intolerance. They provided data from 13 health conditions, with cancer (11 studies), chronic obstructive pulmonary disease (7 studies), fibromyalgia (4 studies), and cystic fibrosis (3 studies) being the most studied. Effective interventions for fatigue included exercise training and physical activities, telerehabilitation and multicomponent and educational interventions. Effective interventions for exercise intolerance included combined aerobic/anaerobic training and integrated disease rehabilitation management. The overall quality of evidence was low to very low and moderate in very few cases. We did not identify CSRs that specifically addressed post-exertional malaise or orthostatic intolerance.

CONCLUSIONS: These results are the first step of indirect evidence able to generate helpful hypotheses for clinical practice and future research. They served as the basis for the three recommendations on treatments for these PCC symptoms published in the current WHO Guidelines for clinical practice.

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KEY WORDS: COVID-19; Rehabilitation; Fatigue; Orthostatic intolerance; Post-acute COVID-19 syndrome

Introduction

This short paper is one of a series reporting the studies developed by Cochrane Rehabilitation for the World Health Organization Rehabilitation Program (WHO-RP) to synthesize the Cochrane evidence relevant to symptoms due to the post COVID-19 condition (PCC).[1] Further details on this work have been reported elsewhere.[2] We focus here on fatigue, post-exertional malaise and orthostatic intolerance.

Among a sample of 1.2 million individuals that experienced symptomatic SARS-CoV-2 infection between 2020 and 2021, 6.2% showed persistent fatigue with bodily pain, cognitive problems, or respiratory problems after three months after the initial infection.[3] Observational studies showed that in Italian COVID-19 inpatients, 53% reported fatigue, and 22% were experiencing chest pain after two months;[4] in a UK cohort of 100 COVID-19-survivors, ongoing fatigue is present after 4-8 weeks in more than two-thirds of them.[5] In addition, Dani *et al*. described a series of patients characterized by debilitating symptoms following the viral infection attributable to orthostatic intolerance.[6] Similarly to chronic fatigue syndrome, it has been proposed that in PCC, too, pro-inflammatory components like cytokines such as IFN gamma and IL-7 are supposed to compromise the regular functioning of the central nervous system,[7, 8] resulting in a wide variety of symptoms mentioned above.

Currently, no evidence exists on specific treatments for such COVID-19 sequelae. However, rehabilitation interventions that proved effective for similar symptoms in other health conditions could be applied to people with PCC as a first meaningful clinical hypothesis (evidence relevant to).[2] With the present review, we aimed to map the current Cochrane evidence on the efficacy of rehabilitation treatments proposed for fatigue, post-exertional malaise and orthostatic intolerance in other health conditions. This information can partially fill the knowledge gap in rehabilitation for people with PCC and help clinicians find the appropriate treatments for individual patients. This information can also generate research hypotheses for further studies.

Evidence acquisition

The design of this study is an overview of reviews with mapping. We reported the methods used in a previous publication.[2] In this short paper, we included Cochrane Systematic Reviews (CSRs) relevant to PCC that considered fatigue, post-exertional fatigue, weakness, post-exertional symptom exacerbation, post-exertional malaise, orthostatic intolerance, postural orthostatic tachycardia syndrome and autonomic nervous system dysfunction, as defined by the WHO. We divided the symptoms into three categories: fatigue, post-exertional malaise and orthostatic intolerance. We summarize the search string in Table I.

Evidence synthesis

Fatigue

We screened 1397 CSRs and excluded 1266 at the title and abstract stage. We screened 131 full texts, with 32 CSR meeting the inclusion criteria (Supplementary Digital Material 1: Supplementary Table I). Participants were adults with cancer (11 CSRs), chronic obstructive pulmonary disease (COPD) (four CSRs), fibromyalgia (four CSRs), chronic kidney disease (two CSRs), cystic fibrosis (two CSRs), multiple sclerosis (two CSRs), bronchiectasis (one CSR), chronic fatigue syndrome (one CSR), chronic respiratory disease (one CSR), facioscapulohumeral muscular dystrophy (one CSR), inflammatory bowel disease (one CSR), interstitial lung disease (one CSR), and traumatic brain injury (one CSR). The methodological quality assessed with AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) was high in all CSRs (Supplementary

TABLE I.—*List of impairments by WHO Rehabilitation Program relevant to post COVID-19 condition and outcomes included in the study.*

Impairment	Synonyms/variations	Outcomes
Fatigue	Fatigue, post-exertional fatigue, exhaustion, weakness[a,b,c]	Any subjective or objective assessment of fatigue (*e.g.*, Chronic Respiratory Questionnaire [CRQ] - fatigue domain; Borg fatigue score; Fatigue Severity Scale)
Post-exertional malaise	Post-exertional symptom exacerbation, post-exertional malaise[c]	Any scale of dyspnea/fatigue/pain assessed after any type of encoded physical effort (*e.g.*, Borg RPE after 6-minutes walking test)
Orthostatic intolerance	Orthostatic intolerance, postural orthostatic tachycardia syndrome, autonomic nervous system dysfunction[d]	Not available Cochrane reviews corresponding to the search criteria

Sources used for the selection of symptoms: a. Systematic Reviews results; b. Global Burden of Disease data; c. WHO clinical case definition development; d. Emerging evidence on underlying pathophysiology of autonomic nervous system dysfunction.

Treatment	Cancer			Stable COPD		Fibromyalgia			CKD		CF		MS	Bronchiectasis			CFS		CRD	FSHMD	IBD	ILD	TBI
Exercise therapy	M*	VL*	na*			M*	VL*	VL*	M*								M*	VL*					
Aerobic and anaerobic training	M*		na*								na*												
Aerobic exercise and strength training																				VL§			
Aerobic exercise						L*		VL*												L§			
Cardiorespiratory exercise programmes																							na*
Whole body vibration + mind exercise							VL*																
Tai chi exercises													VL**										
Yoga	M*		L*																				
Physical activity training	L*	L*	M*																				
Physical activity	M*	na*	L*																				
Physical activity counselling				L*																	VL*		
Physical exercise	M*																						
Pulmonary rehabilitation + exercise training				L*																			
Pulmonary rehabilitation														L*	na*	**na***						na*	
Respiratory muscle training													L**										
Multidimensional survivorship programmes	L*																						
Multicomponent intervention (rehabilitation, care, drugs)				na*																			
Multimodal intervention (exercise + other interventions)	VL*																						
Telerehabilitation																			na*				
Educational interventions	M*		L*																				
E-health educational									na*														
Self-management				L*	L*																		
Acupressure									M§	na**													
Four-wheeled walker				VL§																			
Supervised maintenance programme																							VL*
Transcranial direct current stimulation													VL**										
Transcranial random noise stimulation													VL**										

Figure 1.—Evidence map of fatigue symptom. Lines represent the interventions. Columns represents the health conditions where the searched outcome has been considered. Colors into each cell reported the type of effect (effect against the intervention – black; effect in favor of the intervention – white; no definite results – grey). Quality of evidence was reported into each cell with the following acronyms: VL: very low-quality; L: low-quality; M: moderate-quality; H: high-quality; na: not available.
Comparisons: *Control group; **sham group; §no intervention.
CFS: chronic fatigue syndrome; CKD: chronic kidney disease; IBD: inflammatory bowel disease; CRD: chronic respiratory disease; CF: cystic fibrosis; ILD: interstitial lung disease; COPD: chronic obstructive respiratory disease; FSHMD: facio-scapulo-humeral muscular dystrophy; MS: multiple sclerosis; TBI: traumatic brain injury.

Digital Material 2: Supplementary Table II). The quality of evidence has been evaluated in 23 reviews[9-31] using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) while it was not reported in the others.[32-40]

There is very low- to moderate-quality evidence for fatigue management with rehabilitation comprising exercise training and physical and aerobic activities applied with different frequencies, intensities, duration and types of interventions (Figure 1). Such interventions have been used with benefits (measured through structured questionnaires and self-perception scales) in patients with cancer, fibromyalgia, chronic kidney disease, cystic fibrosis, chronic fatigue syndrome, inflammatory bowel disease and neurological conditions. Studies on fatigue in chronic respiratory diseases (COPD and bronchiectasis, in particular) support (low-quality evidence) the use of pulmonary rehabilitation, multicomponent interventions and telerehabilitation, as well as self- and educational interventions. In addition, educational programs also seem to be effective in cancer patients (low- to moderate-quality of evidence). Finally, acupressure effectively reduced fatigue perception (mea-

Comparisons	Stable COPD		CF
Combined aerobic and anaerobic training			na§
Integrate disease management (including rehabilitation)	na*		
NMES	VL*	VL*	

Figure 2.—Evidence map of post-exertional malaise symptom.
Lines represent the interventions. Columns represents the health conditions where the searched outcome has been considered. Colors into each cell reported the type of effect (effect against the intervention – black; effect in favor of the intervention – white; no definite results – grey). Quality of evidence was reported into each cell the with the following acronyms: VL: very low-quality; L: low-quality; M: moderate-quality; H: high-quality; na: not available.
Comparisons: *Control group; §no intervention.
NMES: neuromuscular electrical stimulation; COPD: chronic obstructive respiratory disease; CF: cystic fibrosis.

sured by the Piper Fatigue Scale) of people with chronic kidney disease, compared to no treatment (moderate-quality of evidence).

Exercise intolerance

We included 4 CSRs (Supplementary Digital Material 3: Supplementary Table III). Participants were adults with stable COPD (3) and cystic fibrosis (1). The results of the AMSTAR 2 assessment indicated the high methodological quality of the CSRs (Supplementary Digital Material 4: Supplementary Table IV). The quality of evidence has been evaluated in two studies[39, 41] using the GRADE approach, while it was not in the other two.[36, 42]

The effective interventions described were combined aerobic/anaerobic training compared to no physical training, integrated disease rehabilitation management compared to control, neuromuscular electrical stimulation (NMES) plus exercise compared to exercise only or NMES compared to usual care. However, only the latter has been demonstrated to promote beneficial effects in terms of endurance time, with very low-quality evidence, in stable COPD (Figure 2).[39]

Orthostatic intolerance and post-exertional malaise

We did not identify CSRs that specifically addressed post-exertional malaise or orthostatic intolerance.

Discussion

This paper maps the current Cochrane evidence on the efficacy of rehabilitation interventions for managing fatigue, post-exertional malaise and orthostatic intolerance in health conditions different from PCC. CSRs focusing on various health conditions showed that fatigue can be effectively managed mainly through various exercise and physical activity modalities. Studies in people affected by chronic respiratory disease or cancer support telerehabilitation, multicomponent and educational interventions. While we did not find CSRs specifically focused on post-exertional malaise and orthostatic intolerance, evidence on the treatment of COPD endorses using NMES as an add-on to exercise training to improve exercise tolerance.

When implementing the "evidence relevant to", we need to check 1) if there are specific pathophysiological mechanisms of PCC suggesting avoiding any of the identified treatments; 2) if there are treatments specific for the reported health conditions that would not be appropriate for PCC. Obviously, in the implementation phase, the need to check individual contraindications in single patients remains. The WHO identified one red flag for PCC rehabilitation: post-exertional symptom exacerbation.[43] This can represent an individual contra-indication for all the treatments considered below.

Findings on exercise and physical interventions align with guidelines that support the integration of exercise training in managing cardiorespiratory, oncological and neurological disorders. There is consensus that such training can benefit the overall quality of life, including fatigue reduction.[44-47] In particular, the 2021 European Society of Cardiology guidelines emphasizes the importance for individuals with chronic conditions to be as active as possible even if they cannot achieve the weekly target of 150 minutes of moderate-intensity physical activity.[44]

In addition to physical activity, we found evidence for the use of telerehabilitation in managing fatigue. Even if it has been studied as a specific intervention, telemedicine is a means to propose different therapies, not a treatment *per se*. Telemedicine has been available for several years,[48] but the COVID-19 pandemic has strongly promoted its development and implementation. A recent systematic review confirms that, with the currently available evidence, telerehabilitation can be considered a feasible and safe option to deliver rehabilitation remotely, providing good continuity of care even in pandemics.[49]

Evidence on the use of self-management and education programs supports the literature promoting patient empowerment to reduce disability and health services utilization (*i.e.* fewer outpatient visits and hospital admissions).[50] These treatments could be appropriate for people with PCC as well.

All the other interventions that showed efficacy for fatigue (acupressure, pulmonary rehabilitation, survivorship programs, transcranial stimulation, walker) or exercise intolerance (NMES as an add-on to exercises) seem highly

correlated to the specific diseases studied in each CSR. For now, they could be regarded as a hypothesis for research but not as clinical solutions in PCC patients.

Looking at the indirect evidence provided with this work and at the current direct evidence coming from the rapid living systematic review produced by Cochrane Rehabilitation,[51, 52] the experts conveyed by the WHO provided the following conditional recommendations for the clinical rehabilitation management of adults with PCC:[43]

• Post-exertional symptom exacerbation: "*education and skills training on energy conservation techniques such as pacing approaches. The provision and training in using assistive products and environmental modifications may be useful for people experiencing moderate to severe PESE*."[43]

• Fatigue: "*a combination of education, skills training on energy conservation techniques such as pacing approaches and, in the absence of post-exertional symptom exacerbation, a cautious return to symptom titrated physical exercise training. The provision and training in the use of assistive products and environmental modifications may be considered for people experiencing levels of fatigue that limit instrumental activities of daily living. Psychological support may be offered to support coping with the symptom*".[43]

• Orthostatic intolerance: "*a combination of education and skills training on self-management strategies and, in the absence of post-exertional symptom exacerbation, physical exercise training. Environmental modifications may be useful to support activities of daily living for people experiencing difficulties with upright positions or standing*".[43]

Also, the WHO proposed a strong recommendation related to the red-flag post-exertional symptom exacerbation: "In adults with post COVID-19 condition exertional desaturation and cardiac impairment following COVID-19 should be ruled out and managed before consideration of physical exercise training. While orthostatic intolerance and post-exertional symptom exacerbation (PESE) are amenable to rehabilitation, their presence will require interventions to be modified in view of these diagnoses for rehabilitation to be safe."[43]

Strengths and limitations of the study

Our map of CSRs focuses on the best current evidence relevant to rehabilitation for people with PCC. However, other high-quality systematic reviews could not be considered in the selection process because they were not included in the Cochrane Library.

We must interpret the findings carefully because very few CSRs showed moderate-quality evidence, while all the others were very low- or low-quality. In addition, the current results did not provide specific evidence on PCC management. Still, they can partially fill the knowledge gap in rehabilitation and help clinicians find the appropriate treatments for individual patients. These findings can also highlight new research priorities for further studies.

Conclusions

Specific rehabilitation interventions successfully used in different health conditions may improve fatigue and exercise intolerance due to PCC. Future research priorities should include producing new and particular evidence on PCC and improving the methodological quality of primary studies in people with chronic diseases. Further, there is a need for CSRs to consider the symptoms of post-exertional malaise and orthostatic intolerance.

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