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SYSTEMATIC REVIEW

Dyspnea: a map of Cochrane evidence relevant to rehabilitation for people with post COVID-19 condition

Claudio CORDANI [1, 2], Stefano G. LAZZARINI [3] *, Elisabetta ZAMPOGNA [4], Matteo J. DEL FURIA [2], Chiara ARIENTI [3], Stefano NEGRINI [1, 2], Carlotte KIEKENS [5]

[1]Department of Biomedical, Surgical and Dental Sciences, University "La Statale", Milan, Italy; [2]IRCCS Istituto Ortopedico Galeazzi, Milan, Italy; [3]IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy; [4]Division of Pulmonary Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS, Tradate, Varese, Italy; [5]IRCCS MultiMedica, Milan, Italy

*Corresponding author: Stefano G. Lazzarini, IRCCS Fondazione Don Carlo Gnocchi, via A. Capecelatro 66, 20148 Milan, Italy.
E-mail: slazzarini@dongnocchi.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 on 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 dyspnea due to PCC.

EVIDENCE ACQUISITION: We searched the last five years' Cochrane Systematic Review (CSRs) using the terms "dyspnea" and its synonyms in the Cochrane Library. We extracted and summarized all 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: We found 371 CSRs published between 2016 and 2021 and included 15 in this overview. We found eight studies on chronic obstructive pulmonary disease, two on cancer, and one for bronchiectasis, chronic respiratory disease, cystic fibrosis, idiopathic pulmonary fibrosis and interstitial lung disease. Effective interventions included pulmonary rehabilitation, also in combination with exercise training, non-invasive ventilation, upper limb training and multicomponent integrated interventions, with very low- to moderate-quality evidence.

CONCLUSIONS: These results are the first step of indirect evidence to generate helpful hypotheses for clinical practice and future research on dyspnea in adults with PCC. They served as the basis for one recommendation on treatments for dyspnea as a PCC symptom published in the current WHO Guidelines for clinical practice.

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KEY WORDS: Post-acute COVID-19 syndrome; Rehabilitation; Physical and rehabilitation medicine; Dyspnea; Signs and symptoms, respiratory.

Introduction

This short paper is part of a series developed by Cochrane Rehabilitation in collaboration with the World Health Organization (WHO) to identify the Cochrane evidence relevant to symptoms due to the post-COVID-19 condition (PCC).[1, 2] We focus here on dyspnea.

Global Burden of Disease Long COVID Collaborators estimated that in a sample of 1.2 million individuals who experienced symptomatic SARS-CoV-2 infection between

2020 and 2021, 3.7% showed persistent respiratory problems.[3] If, on the one hand, the presence of dyspnea can be expected in patients with severe and acute COVID-19 infection,[4] on the other hand, it can be surprising to find this symptom also in patients with only mild infections or in the long-term. Often, the lack of abnormalities in diagnostic imaging and pulmonary function tests makes it hard to explain the causes of dyspnea in non-severe COVID-19 patients who did not experience lung damage and restricted function.[5, 6] Beaudry *et al.* showed that persistent dyspnea after COVID-19 is not associated with definite cardiopulmonary impairment and pinpointed the importance of careful symptom management in these patients.[7] Persistent dyspnea can affect many aspects of patients' lives, deteriorating their functional status, increasing care dependency, triggering anxiety and changing social and family habits.[8]

No specific treatments are suggested for dyspnea in PCC, but several interventions are already being applied in the pulmonary rehabilitation (PR) field.[9, 10] PR mainly includes exercise training and education and is a fundamental intervention for managing chronic obstructive pulmonary disease (COPD) in individuals who remain symptomatic despite optimal medical therapy.[11] PR seems particularly effective in patients with lower exercise tolerance and greater perceived dyspnea on exertion.[12]

With the present review, we aimed to map the current Cochrane evidence on the efficacy of rehabilitation interventions proposed for dyspnea in other health conditions. The findings can partially fill the knowledge gap in PCC-related dyspnea management and help clinicians define appropriate care for these patients. Results from the present study can also contribute to identifying new research hypotheses and priorities for future studies.

Evidence acquisition

We extensively reported the methods used to perform the current mapping in a previous publication.[2] In this study, we included Cochrane Systematic Reviews (CSRs) relevant to PCC that considered dyspnea, shortness of breath, and breathlessness, as defined by the WHO. We summarize the search string in Table I.

Evidence synthesis

We found 371 CSRs and excluded 240 at the title and abstract stage. We screened 131 full texts, with 15 CSRs that met the inclusion criteria (Supplementary Digital Material 1: Supplementary Table I). Participants were adults with stable COPD (8), cancer (2), bronchiectasis (1), chronic respiratory disease (1), cystic fibrosis (1), idiopathic pulmonary fibrosis (1) and interstitial lung disease (1). "A MeaSurement Tool to Assess systematic Reviews" (AMSTAR) 2 showed high methodological quality for all the CSRs included (Supplementary Digital Material 2: Supplementary Table II). Ten reviews evaluated the quality of evidence using the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach,[13-22] while the other five did not report GRADE judgment.[23-27]

We found that PR or exercise training alone can be effectively used (low-quality to moderate-quality evidence) to treat dyspnea in patients with interstitial lung disease, idiopathic pulmonary fibrosis, COPD or cancer, compared to control or no interventions. We found many results on dyspnea in COPD: 1) interventions like upper limb training, multicomponent interventions and non-invasive ventilation (NIV) showed positive effects (not available or low-quality evidence) (Figure 1); 2) treatments that did not result effective (very low- to moderate-quality evidence) included neuromuscular electrical stimulation (compared to active exercises, sham or no stimulation), physical activity counselling combined with PR or optional exercises (compared to no intervention or optional exercises alone), singing (compared to no intervention, handcraft or film workshop), supervised maintenance program (compared to usual care) (Figure 1); 3) behavior modification and self-management (*e.g.* group-based activities focusing on the benefits of physical activity, breathing and energy-conservation techniques, stress-management techniques and healthy habits) combined with exercise training and drugs can be effective (low- and moderate-quality evidence) (Figure 2); 4) other treatments (active mind-body movement therapies, in-person physical activity counselling interventions, inspiratory muscle training and NIV) added to PR did not provide significant benefits compared to PR or supervised exercises alone (Figure 2). In addition, over-

TABLE I.—*Impairment, related symptoms and outcomes relevant to post COVID-19 condition included in the study, as identified by WHO Rehabilitation Program.*

Impairment	Synonyms/variations	Outcomes
Breathing impairment	Dyspnea, dyspnea, shortness of breath, breathlessness	Any subjective or objective assessment of dyspnea (e.g., Chronic Respiratory Disease Questionnaire - dyspnea domain; Borg CR10; Transition Dyspnea Index)

Sources used for the selection of symptoms: systematic reviews results, Global Burden of Disease data and WHO clinical case definition development.

Treatment	Stable COPD	Cancer	Chronic respiratory diseases	Interstitial lung disease	Idiopathic pulmonary fibrosis
Pulmonary rehabilitation				L*	L*
Pulmonary rehabilitation/exercise training	M§				
Exercise training		L* VL*			
Upper limb training	M**				
Integrated disease management	na*				
Multicomponent intervention (rehabilitation, organization of care, pharmacotherapy)	na*				
Non-invasive ventilation	**na*** na* na*				
Neuromuscular electrical stimulation	VL*				
Physical activity counselling	L§				
Singing	VL*				
Supervised maintenance programme	na*				
Telerehabilitation			L*		

Figure 1.—Evidence map of interventions for dyspnea symptom compared to control, sham intervention, no therapy. Lines represent the interventions. Columns represent 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.
*Control group; **sham group; §no intervention. COPD: chronic obstructive respiratory disease.

Figure 2.— Evidence map of interventions for dyspnea symptom in addition to other treatments compared to other treatments alone. Lines represent the interventions. Columns represent 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.
COPD: chronic obstructive respiratory disease.

Treatment studied	Adjunct treatment	Stable COPD
Exercise training and drugs	Behavior modification	M
Exercise training and drugs	Behavior modification and drugs	M M
Structured exercise training	Self-management	L L
Active mind-body movement therapies	Pulmonary rehabilitation	VL
In-person physical activity counselling intervention	Pulmonary rehabilitation	L
Inspiratory muscle training	Pulmonary rehabilitation	M
Non-invasive ventilation	Pulmonary rehabilitation	L
Physical activity counselling intervention	Optional supervised exercise	L

Treatment	Comparison	Stable COPD	Bronchiectasis	Chronic respiratory diseases	Cystic fibrosis
NIV in overnight ventilation	Room air				na
NIV in overnight ventilation	Oxygen				na
Pulmonary telerehabilitation	Pulmonary rehabilitation			L	
Active mind-body movement therapies	Pulmonary rehabilitation	VL			
Web-based pulmonary rehabilitation	Pulmonary rehabilitation	L			
Oscillatory PEP therapy	Active cycle of breathing technique with gravity-assisted drainage		L		
Water-based exercise training	Land-based exercise training	L			

Figure 3.—Evidence map of interventions for dyspnea symptom compared to other interventions. Lines represent the interventions. Columns represent 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.
COPD: chronic obstructive respiratory disease; NIV: non-invasive ventilation; PEP: positive expiratory pressure.

night NIV significantly reduced dyspnea perception compared to room-air ventilation in cystic fibrosis patients. However, the same intervention was not superior to oxygen supplementation in the same population (Figure 3).

In patients with stable COPD, bronchiectasis and chronic respiratory diseases, we did not find significant effects of pulmonary telerehabilitation, active mind-body movement therapies, or web-based PR compared to PR, nor of

oscillatory positive expiratory pressure therapy compared to active cycle of breathing technique and water-based compared to land-based exercise training (very low- and low-quality evidence) (Figure 3).

Discussion

This paper mapped the Cochrane evidence relevant to PCC dyspnea management in different health conditions. Considering CSRs that included people with COPD, cancer, bronchiectasis, chronic respiratory disease, cystic fibrosis, idiopathic pulmonary fibrosis and interstitial lung disease, we found PR or exercise training alone can effectively manage dyspnea. Studies on people affected by COPD and cystic fibrosis supported using NIV (for reducing symptom perception), upper limb training and multicomponent integrated intervention.

When implementing the "evidence relevant to", we need to check if 1) 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.[28] This can represent an individual contra-indication for all the treatments considered below.

Our results on PR and integrated programs confirm the recommendations of different clinical guidelines focused on respiratory diseases suggesting their use to improve dyspnea and health status in a clinically relevant way.[29, 30] PR increases inspiratory volume and reduces dynamic hyperinflation, reducing task-related dyspnoea.[31] Also, exercise training, alone or as part of PR interventions, seems beneficial in respiratory and oncological conditions. Similarly to what we observed for fatigue in a previous CSR mapping on PCC,[32] the use of exercise training supports the expert consensus and practical recommendations that consider such intervention as a cornerstone in reconditioning pathways.[29, 33, 34]

The positive effects observed from the application of upper limb training programs might be due to an increased arm exercise capacity, including the improved aerobic capacity of the upper limb muscles, desensitization or tolerance to dyspnea during arm activity, increased force-generating capacity of the muscles of the upper limb and improved muscular coordination.[35]

The effectiveness of interventions based on behavioral modification and self-management, in line with similar findings on PCC fatigue,[32] support the hypothesis that such kind of approaches can prevent patients (with respiratory diseases, in particular) from catastrophizing and misinterpreting dyspnea which in turn increases discomfort and creates a loop that heightens anxiety.[36, 37]

Finally, results of NIV application in respiratory disorders suggest that this tool can play an important role in managing chronic respiratory failure by reversing or stabilizing hypercapnia and hypoxemia through improving alveolar ventilation and the reduction of respiratory muscle fatigue.[38, 39]

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,[40-42] the experts conveyed by the WHO provided the following conditional recommendation for the clinical rehabilitation management of adults with breathing impairment due to PCC:[28]

• we suggest using a combination of education and skills training on self-management strategies such as nasal breathing and pacing approaches and, in the absence of post-exertional symptom exacerbation, physical exercise training. Breathing control techniques could be offered to those presenting with a suboptimal breathing pattern, and psychological support may be useful to address contributing factors such as anxiety.[28]

Our map of CSRs focuses on the best current evidence relevant to dyspnea in the rehabilitation of 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 need to interpret the findings carefully because most CSRs provided very low- and low-quality evidence. These aspects need improvement in necessary future studies. An exception might be the study on PR efficacy compared to unsupervised activities, general practitioners' care, general advice and no interventions, which has been consistently confirmed in the literature.[43] In addition, our study did not provide evidence on PCC dyspnea management specifically but can fill, at least partially, the current knowledge gap in the field. These findings can be helpful for clinicians in delivering more appropriate treatments to individual patients and promote the development of new dedicated studies.

Conclusions

Specific rehabilitation interventions that have been successfully used in different health conditions may improve

dyspnea management in PCC. Future research priorities are the improvement of the methodological quality of primary studies in people with chronic diseases and the production of new and specific evidence on PCC.

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