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SYSTEMATIC REVIEW

Cognitive impairment, anxiety and depression: a map of Cochrane evidence relevant to rehabilitation for people with post COVID-19 condition

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ABSTRACT

INTRODUCTION: Currently, no evidence exists on specific treatments for post COVID-19 condition (PCC). However, rehabilitation interventions that are effective for similar symptoms in other health conditions could be applied to people with PCC. With this overview of systematic reviews with mapping, we aimed to describe the Cochrane evidence on rehabilitation interventions proposed for cognitive impairment, anxiety and depression in different health conditions that can be relevant for PCC.

EVIDENCE ACQUISITION: We searched the last five years' Cochrane Systematic Review (CSRs) using the terms "cognitive impairment," "depressive disorder," "anxiety disorder," their synonyms and variants, and "rehabilitation" 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: We found 3596 CSRs published between 2016 and 2021, and we included 17 on cognitive impairment and 37 on anxiety and depression. For cognitive impairment, we found 7 CSRs on participants with stroke, 3 with cancer, 2 with Parkinson's disease, and one each for five other health conditions. Each intervention improved a different domain, and included exercises, cognitive and attention-specific training, and computerized cognition-based training (from very low to high-quality evidence). For anxiety and depression, we found 10 CSRs including participants with cancer, 8 with stroke, 3 with chronic obstructive pulmonary disease, and 2 or 1 each in 11 other health conditions. Exercise training, physical activity and yoga resulted effective in several pathologies (very low- to moderate-quality evidence). In specific diseases, we found effective acupuncture, animal-assisted therapy, aromatherapy, educational programs, home-based multidimensional survivorship programs, manual acupressure massage, memory rehabilitation, non-invasive brain stimulation, pulmonary rehabilitation, and telerehabilitation (very low- to moderate-quality evidence).

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: Post-acute COVID-19 syndrome; Rehabilitation; Anxiety; Depression; Cognitive dysfunction.

Introduction

Cochrane Rehabilitation in collaboration with the World Health Organization (WHO) launched a series of short papers that report on Cochrane evidence on common post COVID-19 condition (PCC) symptoms.[1, 2] This short study focuses on cognitive impairment, depression, and anxiety related to PCC.

The Global Burden of Disease Long COVID Collaborators estimate that 6.2% of SARS-CoV-2 infection survivors experience long COVID (currently named PCC by the WHO) cluster symptoms that include neurological manifestations, such as cognitive impairment, and mental health conditions, such as depression and anxiety.[3, 4] Objective assessments revealed lower Montreal Cognitive Assessment (MoCA) scores among individuals with PCC compared with healthy controls, which suggests global cognitive deficits (*i.e.*, attention/processing speed, executive functioning, language, and memory).[5-7]

Regarding anxiety and depression, self-reported symptoms remain frequent;[8, 9] however, the current understanding of the chronology of COVID-19 severity and the onset of mental health conditions remains uncertain, and it shifts between different schools of thought.[10] A recent report of 54,442 participants found an associations between COVID-19 infection and psychological distress, not related to sex, education, ethnicity, or pre-existing mental health conditions.[10] Rather than being caused by SARS-CoV-2 infection, the findings suggested that depression and anxiety symptoms may have been triggered by the pandemic, fear of infection, and drastic changes in social interactions and other environmental factors.[10] In contrast, a PCC multisite study revealed a correlation between sociodemographic factors (older age, lower education level), pre-existing neurological conditions, and lower cognition in people with PCC.[7, 11] Because no association has been detected between infection severity and PCC, it is possible that sociodemographic factors and mental health status exacerbate both COVID-19 severity infection and PCC symptoms.[7] Finally, psychological distress is linked to chronic immune suppression and chronic systemic inflammation, leading to a constant production of proinflammatory cytokines.[12-15] Literature shows that both immune suppression and proinflammatory cytokines are associated with PCC symptoms. Hence, it has been proposed that a pre-existing diagnosis of depression and/or anxiety may lead to PCC symptoms.[16]

Guidelines for treating cognitive impairment and other mental health conditions following COVID-19 infection are currently under development; general recommendations include a multidisciplinary approach and rehabilitation strategies.[17] The primary aim of this work is to map the current Cochrane evidence on the efficacy of rehabilitation interventions recommended for cognitive impairment, anxiety, and depression, which are manifested in different primary conditions, to help merge the present knowledge gap. The findings will 1) encourage the adaptation or development of novel rehabilitation models; and 2) stimulate future research efforts.

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 cognitive impairment, anxiety and depression, as defined by the WHO.[1] We divided the symptoms into two categories: cognitive impairment, and anxiety and depression. We summarize the search strings in Table I.

Evidence synthesis

The findings were grouped into two final evidence maps: neurological disorder – cognitive impairment (Figure 1), and psychological conditions – anxiety and depression (Figure 2).

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
Cognitive impairment	Cognitive impairment, attention deficit, memory impairment, concentration impairment, executive dysfunction, cognitive communication disorder	Any subjective or objective assessment of the specified cognitive domains, or overall cognitive status if not available
Anxiety and depression	Depressive anxiety syndrome, depressive disorder, anxiety disorder, anxieties	Self-assessed questionnaires and patient-reported outcomes

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

Treatment	Stroke		Cancer		PD	Cognitively healthy people in midlife		Dementia		Healthy ageing	MCI	Schizophrenia	
Attention													
Attention training	VL-M*	VL-L*											
Cognitive training					L*			VL-L*	VL-L*				
Communication													
Caregiver-mediated exercises	VL*												
Cognitive training								VL-L*	VL-H*				
Computerised cognitive training										L*	VL*		
Memory training	M*												
Exercises	na*												
tDCS plus SLT	L-M*	VL-L*											
Telerehabilitation	na*												
Executive function													
Cognitive training					L*	L*		VL-L*					
Computerised cognition-based training										L*	VL*		
Global cognitive function													
Attention training	VL*												
Cognitive training					L*			VL-M*					
Computerised cognitive training											VL*		
Exercises	na*		M*	L*									
Home-based multidimensional survivorship programmes			na*										
Videogames												L*	**L***
tDCS	L*												
Memory													
Caregiver-mediated exercises	VL*												
Cognitive training					L*			VL-L*					
Computerised cognition-based training						L*	**L***			L*	VL-L*		
Exercises	na*												
Processing speed													
Cognitive training					L*			VL-L*					
Computerised cognition-based training										VL*			

Figure 1.—Evidence map of interventions for cognitive impairment.
Lines represent the interventions. Columns represent the health conditions where the searched outcome has been considered. Colors in 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 in each cell with the following acronyms: VL: very low-quality; L: low-quality; M: moderate-quality; H: high-quality; na: not available. *compared to control, sham or other intervention.
PD: Parkinson's disease; MCI: mild cognitive impairment; tDCS: transcranial direct current stimulation; SLT: speech and language therapy.

Cognitive impairment

We screened 1642 CSRs, excluding 1510 at the title and abstract stage. We screened 132 full texts, with 17 CSRs that met the inclusion criteria (Supplementary Digital Material 1: Supplementary Table I). Participants in 7 studies had stroke, in 3 cancer, in 2 Parkinson's disease, and one each for cognitively healthy people in midlife, dementia, healthy aging, mild cognitive impairment and schizophrenia. Assessment of multiple systematic reviews (AMSTAR) 2 reported a high methodological quality for the CSRs included (Supplementary Digital Material 2: Supplementary Table II). Except for four CSRs,[18-21] the reviews evaluated the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[18-36]

Attentional domain can be effectively approached with cognitive and attention-specific training (very low- to low-quality evidence). Cognitive training was identified as a useful rehabilitative intervention for the management of communication, executive function, memory, and global cognitive dysfunctions (very low- to high-quality evi-

Intervention	Cancer						Chronic fatigue syndrome	Chronic kidney disease		Chronic respiratory disease		COPD	Dementia	Depression	Fibromyalgia	MCI	MS	Stroke		TBI
Acupressure								VL	VL					L						
Animal-assisted therapy													L							
Aromatherapy massage	VL																			
Attention training																		L		
Cardiorespiratory training																		na		VL
Cognitive training															L	VL				
Computerised cognitive training																VL				
Educational intervention	L			VL																
Exercise therapy							VL													
Home-based multidimensional survivorship programmes	L			VL																
Integrated disease management												na								
Massage	VL																			
Mixed training																		na		
Non-invasive brain stimulation																		VL		
Occupational therapy																		L		
Physical activity	M	L	VL	na	L	VL														
Pulmonary telerehabilitation										na	na									
Resistance training																		na		
Singing												na								
Telerehabilitation																		M		
tDCS																	VL			
Work-directed intervention														M						
Work-directed plus clinical intervention														L						
Yoga	L			VL														VL	VL	

Figure 2.— Evidence map of interventions for anxiety and depression compared to control, sham or other intervention.
Lines represent the interventions. Columns represent the health conditions where the searched outcome has been considered. Colours in each cell reported the type of effect (effect against the intervention – black; effect in favour of the intervention – white; no definite results - grey). Quality of evidence was reported in each cell with the following acronyms: VL=very low-quality; L=low-quality; M=moderate-quality; H=high-quality; na: not available.
CFS: chronic fatigue syndrome; CKD: chronic kidney disease; CRD: chronic respiratory disease; COPD: chronic obstructive respiratory disease; MCI: mild cognitive impairment; MS: multiple sclerosis; TBI: traumatic brain injury.

dence). Exercise seems to improve overall cognitive functions (low-quality evidence), while computerized cognition-based training was effective for memory impairment (Figure 1).

Anxiety and depression

We screened 1954 CSRs, excluding 1900 at the title and abstract stage. We screened 54 full texts, with 37 CSRs that met the inclusion criteria (Supplementary Digital Material 3: Supplementary Table III). Participants in 10 studies were adults with cancer, 8 with stroke, 3 with chronic obstructive pulmonary disease (COPD), 2 each with chronic kidney disease, dementia, depression, mild cognitive impairment, and multiple sclerosis, and 1 each with chronic fatigue syndrome, chronic pelvic pain syndrome, chronic respiratory disease, fibromyalgia, osteoarthritis, and traumatic brain injury. AMSTAR 2 assessment reported a high methodological quality for the CSRs included (Supplementary Digital Material 4: Supplementary Table IV). Thirty reviews evaluated the quality of evidence using the GRADE approach,[33, 35, 37-57] while seven did not report the assessment.[34, 58-63]

Exercise training, physical activity and yoga resulted effective in several pathologies like multiple sclerosis, stroke, osteoarthritis, chronic fatigue syndrome, chronic kidney disease, chronic pelvic disorders, and cancer (very

low- to moderate-quality evidence). Animal-assisted therapy improves symptoms in dementia patients with low-quality evidence. Aromatherapy, massage and educational programs, and home-based multidimensional survivorship programs showed positive results in cancer patients with very low- to low-quality evidence. Memory rehabilitation showed positive effects in multiple sclerosis (moderate-quality evidence). Pulmonary rehabilitation and telerehabilitation programs benefit patients with chronic respiratory disorders. Acupuncture added to other treatments, and manual acupressure were found to be effective in depression and stroke (very low- to low-quality evidence). Finally, non-invasive brain stimulation in stroke patients seems to provide beneficial effects on symptoms of anxiety and depression with very low-quality evidence (Figure 2).

Discussion

The present study mapped the Cochrane evidence on different health conditions that could be relevant to the management of cognitive impairment, anxiety, and depression symptoms in people with PCC.

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; and 2) 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 symptoms exacerbation.[64] This can represent an individual contra-indication for some of the treatments considered below.

Cognitive impairment can be caused by different treatable illnesses; in our search, we found interventions for a large subset of the most common diseases affecting memory and thinking. Memory training is the most effective treatment to improve memory following stroke.[36] We noted that tDCS plus SLT and cognitive training may have a high-to-moderate effect on communication, global cognition, and memory in people with dementia and in patients recovering from stroke.[18, 21] However, the evidence on communication is limited because the benefits were detected in only one subset (verbal fluency), and it is unclear whether the benefits are maintained in the long term.[18] Furthermore, the effectiveness is inconsistent regarding cognitive training when compared with other treatments in controls or when applied to a different population, such as individuals with Parkinson's disease.[28] Only two comparisons were found targeting people with mild cognitive impairment (MCI), and the quality of evidence was low to very low.[31] This is worrisome when considering that one-third of people with MCI develop dementia within the first 1-5 years after diagnosis.[65, 66]

Although the long-term outcome of cognitive impairment in PCC remains uncertain at this time, some scientists have postulated that Alzheimer's disease and SARS-CoV-2 infection exhibit similar early pathogenic traits linked to hypometabolic changes in the brain prior to the development of atrophy.[67] Furthermore, positron emission tomography (PET) scans performed on patients with PCC reveal cellular metabolic stress, which is an early marker of dementia.[67] Currently, there are nine registered trials assessing the effectiveness of cognitive training on memory and thinking among patients with PCC.[68] Based on our findings, and the low adverse events registered with these interventions, we feel confident that implementing cognitive training into the post-recovery multidisciplinary rehabilitation program would mitigate the decline in cognition and improve patients' quality of life.

A larger body of research reported that COVID-19 survivors experience a variety of psychological issues, such as depression and anxiety, that impact post-traumatic growth.[69, 70] Hospitalization experiences (*i.e.*, witnessing the challenges faced by other COVID-19 patients and a lack of mental health interventions during the post-acute phase) may correlate with a higher chance of developing depression; also, sociodemographic characteristics, being a parent, hospitalization experiences, and social stigma may induce anxiety.[69, 71] We identified only four CSRs investigating psychological treatments for individuals who experienced pulmonary or chronic respiratory disease, and the quality of evidence was low to very low.[45, 60-62]

Telerehabilitation may be a promising method to provide continuous service post recovery and after discharge, but factors such as accessibility, cost, motor impairment, skills and culture may hinder patient satisfaction. Likewise, slow return to physical activity may produce psychological benefits among patients with PCC.[72] Physical activity has been found to be a safe and effective intervention among vulnerable adults, and it bestows protection against global functional deterioration.[73, 74] Depression worsens cognitive impairment and mental fogginess; therefore, offering a tailored exercise program that meets the physical and psychological recovery needs of this population would contribute to enhanced cognitive and psychological well-being. It is critical that physical and psychological treatments are offered in a timely manner and as a continuum to reduce the long-term effects of COVID-19.[75]

Looking at the indirect evidence provided with this research and at the current direct evidence coming from the rapid living systematic review produced by Cochrane Rehabilitation,[76-78] the experts conveyed by the WHO provided the following conditional recommendations for the clinical rehabilitation management of adults with PCC:[64]

• cognitive impairment: a combination of education, skills training on self-management strategies and cognitive exercises. The provision and training in the use of assistive products and environmental modifications may be useful to address the cognitive dysfunctions as they apply to daily functoning.[64]

• anxiety and depression: psychological support and, in the absence of post-exertional symptoms exacerbation, physical exercise training. In addition, mindfulness-based approaches and peer support groups may be useful to reduce distress in some people with PCC when managing long-term symptoms.[64]

Our map of CSRs focused on the best current evidence relevant to cognitive impairment, depression, and anxiety in people with PCC. The authors recognize that other high-quality systematic reviews were not included in this analysis; therefore, evaluation of other potentially effective interventions is missing. We must interpret the findings carefully due to the inclusion of several CSRs presenting low-quality evidence, and future studies should reflect higher methodological quality to increase the quality of the evidence. While we transition from researching treatments for COVID-19 to evaluating the effectiveness of interventions post-discharge and during recovery, the findings gathered from this evidence map will support clinical management while researchers continue to examine additional interventions for this specific population.

Conclusions

A limited number of interventions, such as cognitive training, telerehabilitation, and physical activity, have positive effects on cognitive impairment, depression, and anxiety in different clinical sequelae and may support the reduction of cognitive and psychological symptoms in PCC. Future studies should aim to broaden their scope regarding the analysis of interventions specific to PCC.

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