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Pulmonary rehabilitation for people with chronic obstructive pulmonary disease

A protocol for an overview of Cochrane reviews

Zênia T.S. Araujo, MSc[a,*], Karla M.P.P. Mendonça, PhD[b], Bruma M.M. Souza, BSCE[c], Tacito Z.M. Santos, MSc[d], Gabriela S.S. Chaves, PhD[e], Brenda N.G. Andriolo, PhD[f], Patricia A.M.S. Nogueira, PhD[g]

Abstract

Background: Pulmonary rehabilitation (PR) is an indispensable component in the nonpharmacological management of patients with chronic obstructive pulmonary disease (COPD) with significant improvements in quality of life and exercise capacity. It is strongly supported by systematic reviews (SR) as part of the treatment of these patients. However, it is not known which PR components are essential, such as duration, ideal locations, type and intensity of training, degree of supervision, adherence, cost-effectiveness challenge, and how long the program effects last. This overview aims to evaluate and describe different pulmonary rehabilitation interventions for individuals with COPD.

Methods: Only systematic reviews of randomized controlled trials (RCTs) published in the Cochrane Database of Systematic Reviews will be included. The following results were analyzed: health-related quality of life, functional capacity, mortality, dyspnea, cost-effectiveness, and adverse events. The risk of bias will be assessed by the Risk of Bias in Systematic Reviews (ROBIS). The methodological quality will be analyzed through the Assessment of Multiple Systematic Reviews (AMSTAR-2). We will use the evaluations of the Classification of Recommendations, Evaluation, Development and Evaluation (GRADE) of the authors of the included systematic reviews. The screening of systematic reviews, eligibility evaluation, data extraction, methodological quality, and quality of evidence will be performed in pairs by independent reviewers. The results that have been reported in the included reviews will be summarized in an "Overview of Reviews" table. The main conclusions about the effects of the interventions studied in the included reviews will be summarized and organized in clinically meaningful categories.

Results: The article in this overview will be submitted for publication in a peer-reviewed journal. The results will also be included in a doctoral thesis and disclosed in medical conferences.

Conclusions: We expect to compile evidence from multiple systematic reviews of pulmonary rehabilitation in people with COPD in an accessible and useful document.

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Abbreviations: AMSTAR-2 = Assessment of Multiple Systematic Reviews-2, COPD = chronic obstructive pulmonary disease, GRADE = Classification of Recommendations, Evaluation, Development, and Evaluation, PR = pulmonary rehabilitation, RCTs = randomized controlled trials, ROBIS = risk of bias in systematic reviews, SR = systematic reviews.

Keywords: chronic obstructive pulmonary disease, overview, pulmonary disease, pulmonary rehabilitation, therapeutic exercise

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[a] Laboratory of measures and evaluation in health, [b] Postgraduate Course in Physiotherapy of the Federal University of Rio Grande do Norte, Natal, Brazil, [c] University of New Hampshire, Durham, NH, [d] Laboratory of evaluation and respiratory intervention, Department of Physiotherapy, [e] School of Kinesiology and Health Science, York University, Toronto, Canada, [f] Cochrane Brazil, Center for Evidence-Based Health Studies and Technology Assessment in Health, São Paulo, [g] Laboratory of measures and evaluation in health, Postgraduate Course in Physiotherapy of the Federal University of Rio Grande do Norte, Natal, Brazil.

[*] Correspondence: Zênia T.S. Araujo, Av. esperança, 189 Apt. 801, Manaíra, CEP: 58038-280 João Pessoa – PB, Brazil (e-mail: zeniatsa@gmail.com).

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a frequent disease, determined by constant respiratory symptoms and chronic airflow limitation. It is clinically determined due to exacerbations, comorbidities, and symptoms, such as: dyspnoea, cough, and/or expectoration. Chronic airflow limitation is a characteristic of COPD and is caused by airway and/or alveolar abnormalities.[1–4] The diagnosis requires confirmation by spirometry ($FEV_1/FVC \leq 70\%$ post-bronchodilator or $FEV_1/FVC \leq 70\%$ and $FEV_1 < 80\%$ pre-bronchodilator—where post-bronchodilator testing is not possible) and history of exposure to particulate matter or harmful gases.[5–10]

The data indicate worldwide a high prevalence of COPD with projections of increase over the next 30 years, with estimated annual mortality of >45 million people.[1,11] As a prevalent disease, COPD is also associated with comorbidities, with a high degree of disability and with a consequent financial burden, implying in significant consequences for health and the economy.[12–15] These factors have a major impact on health and economy and make it a major challenge for managers.[16,17]

Thus, considering the current scenario of pathophysiological and functional changes in COPD, we have been looking for more effective pharmacological and non-pharmacological strategies in the management of these patients. Within these approaches, pulmonary rehabilitation programs,[1,18,19] according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS), stand out as "a comprehensive intervention based on a comprehensive patient assessment followed by patient-tailored therapies, which include, but are not limited to, physical training, education, and behavior change, aimed at improving the physical and psychological condition of people with chronic respiratory disease and promoting adherence long-term health-enhancing behaviors."[19]

Emphasis is given to the physical training that can be performed in groups, but with individualized sessions that involve aerobic, resistance, interval or continuous exercises, resistance/strength, flexibility, neuromuscular electrical stimulation, exercises that involve the upper and lower limbs, in addition to inspiratory muscle training.[1,9,19] Pulmonary rehabilitation can be performed in different settings, such as: hospital, outpatient clinic, or home.[18–21] The evidence[9,22,23] points to the inclusion in the rehabilitation of these patients with COPD at all levels of severity of impairment of pulmonary function, especially in moderate to severe pulmonary function.

The inclusion of people with COPD in these programs should be based on symptoms and functional limitations, rather than just on the severity of lung impairment,[1,19,24] such as: exertional dyspnea secondary to ventilatory impairment,[25] low levels of physical activity and depression,[26–28] comorbid conditions such as cardiovascular and cerebrovascular diseases, endocrine and metabolic disorders, psychiatric and neurological disorders, gastrointestinal disorders, musculoskeletal disorders,[29] exacerbations of the disease, and impairment of quality of life.[1,6,9]

Thus, the evidence indicates the following physiological benefits of the physical training component in pulmonary rehabilitation in patients with COPD: decrease in circulating inflammatory markers,[30–32] better supply of oxygen to respiratory and peripheral muscles,[33] increased carbon monoxide diffusion capacity, and effort tolerance.[31]

Therefore, the benefits of pulmonary rehabilitation in patients with COPD are related to clinical improvement directly reflected in health-related quality of life, dyspnea, fatigue, emotional function, and exercise capacity according to Cochrane systematic review and meta-analysis,[18] as well as the current clinical guidelines.[1,6,19]

In recent years the number of Cochrane systematic reviews has been increasing, which addresses pulmonary rehabilitation in patients with COPD, and directly reflects the assistance model focused on approaches that aim to modify the behavior of this population. These Cochrane reviews point to different models in providing care that involves the traditional inpatient or outpatient model as alternative models in the community or at home.[1,6,18,23]

Despite all the advances in pulmonary rehabilitation, there are still issues to be improved, as: to increase patient access to rehabilitation programs around the world; to understand effects during hospitalization due to exacerbation and/or after early exacerbation (within 1 month of exacerbation); benefits in the early stage of COPD (mild disease); alternative models of pulmonary rehabilitation (use of new technologies, telerreabilitation, home rehabilitation, use of minimal equipment or without equipment, self-management); degree of supervision; intensity of exercises; ideal time, and duration of the effects of rehabilitation.[18,34]

Understanding these issues can be useful in guiding therapeutic and policy decisions (e.g., health-related quality of life impacts, functional capacity, cost-effectiveness, adverse events) in a single, scientifically accessible document to provide a "friendly front end," so that the reader does not have to assimilate the data from separate systematic reviews.[35] Thus, this overview aims to summarize the evidence from the different available models of pulmonary rehabilitation interventions for COPD patients, to identify evidence gaps in the current literature to inform about new titles for systematic review of pulmonary rehabilitation, and to describe pulmonary rehabilitation interventions that patients with COPD.

2. Methods

It is an overview protocol that follows the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[36] This protocol was recorded in the Prospective International Registry of Systematic Review (PROSPERO), registration number CRD42019111564. (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=111564).

2.1. Criteria for inclusion of revisions

2.1.1. Types of study. For this overview, only systematic reviews of randomized controlled trials (RCTs) for pulmonary rehabilitation in people with COPD, published in the Cochrane Database of Systematic Reviews, will be included. This overview seeks to assess the evidence published in Cochrane original systematic reviews and will not attempt to update these reviews. However, specific information on intervention components can be requested from test reports and individual researchers.

2.1.1.1. Inclusion criteria. For the purposes of this overview, systematic reviews evaluating pulmonary rehabilitation including physical training (e.g., aerobic exercise, resisted exercise or aerobic, and resisted exercise) will be included; educational component and/or psychological support such as intervention. Supervised or unsupervised interventions will be included in a rehabilitation center, hospital, or home.[1,3,9]

2.1.1.2. Exclusion criteria. We will exclude reviews of non-pharmacological treatments and treatment devices that are beyond the scope of this overview.

2.1.2. Participants/population. Cochrane reviews of people with COPD diagnosed based on clinical and/or spirometric criteria[1,2,9] will be included. Adults (18 years of age or older) without any restrictions based on the severity of the disease or in the exacerbated state. In this overview we will consider the standardized by review authors from "valid" concepts.

2.1.3. Intervention. Systematic reviews that evaluated pulmonary rehabilitation including physical training (e.g., aerobic exercise, resisted exercise or aerobic, and resisted exercise); educational component and/or psychological support such as intervention. Supervised or unsupervised interventions will be included in a rehabilitation center, hospital, or home.[1,3,9]

2.1.4. Comparator (s)/control. Any control considered for comparison in individual systematic reviews. This includes other treatments, no treatment, or placebo.

2.1.5. Outcomes

2.1.5.1. Primary outcomes.

- Health-related quality of life (HRQoL) (measured by Saint George's Respiratory Questionnaire, Clinical COPD Questionnaire, 36-Item Short Form Health Survey questionnaire, COPD Assessment Test, or any validated instrument);
- Functional capacity (measured by cardiopulmonary exercise test—CPET; shuttle walk tests—SWTS; 6 minute walk test—6MWT, or any other validated instrument);
- Mortality.

2.1.5.2. Secondary outcomes.

- Dyspnea (as measured by MRC, Borg, or any other validated instrument);
- Cost-effectiveness;
- Adverse events (hospitalizations, absenteeism, at work, exacerbations).

2.2. Research methods to identify revisions

The searches will be conducted in the Cochrane Systematic Reviews Database (CDSR), in the Cochrane Library. The search strategy is presented in Supplementary Digital Content (Appendix 1, http://links.lww.com/MD/D237). Non-cochrane reviews will not be considered or redeemed for this overview. We will note when the included reviews are outdated, whether new relevant studies have been published, and whether there is any relevant intervention for which a systematic review has not yet been published. However, updates to systematic reviews or new systematic reviews should not be performed within the overview. We will not apply date or language restrictions. All protocols for revisions will be noted in the "Studies awaiting evaluation" section for possible inclusion in future updates of this overview.

2.3. Collection and analysis of data

2.3.1. Selection of revisions. Two authors of this overview (ZTSA and TZMS) will independently evaluate all revisions retrieved through the eligibility survey using the criteria listed above under criteria for considering revisions for inclusion. We will resolve all conflicts through discussions to reach a by a third party.

2.3.2. Extraction and management of data. Data extraction from each included revision will be performed independently by 2 authors (ZTSA and TZMS) using Review Manager 5.3.5 (the Cochrane Collaboration, London, United Kingdom).[37] Possible disagreements will be resolved by a third author (PAMSN) of the overview. From each of the included reviews, relevant data such as the number of trials included, the number of participants included, the date of the last survey, and the inclusion and exclusion criteria will be extracted. The characteristics such as population, intervention (pulmonary rehabilitation) and dose (frequency/intensity), adherence, update check, comparison, control description, outcomes, and limitations of the review will also be presented in a Table 1 containing "Characteristics of included reviews."

2.4. Evaluation of the methodological quality of the included revisions

2.4.1. Quality of included revisions. Two authors of the overview (ZTSA and GSSC) will independently evaluate the methodological quality in each review included to assess whether they met the criteria specified in the "Assessment of Various Systematic Reviews" (AMSTAR-2).[38] Disagreements will be resolved through discussion between them and with the arbitration of a third general author (PAMSN) if necessary. The results of the methodological quality assessment of the included reviews will be included in an additional Table 2.

2.4.2. Risk assessment of bias. Two review authors (ZTSA and GSSC) will independently assess the risk of bias of the included revisions using the bias risk tool in systematic reviews (ROBIS).[39] We will present in a Table 3 the assessment of individual ROBIS items or domains (along with justification for judgments for each evaluation—relevance, identification of potential bias risks during the review process, and general bias risk).

Risk of bias evaluation will be used to conduct sensitivity analyzes, but we will not rule out revisions based on bias assessment risk. We will summarize this information in accordance with the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions.[40]

2.4.3. Quality of evidence in included reviews. The strength of the evidence or the overall quality of the evidence provided in the included reviews will be evaluated using the GRADE approach as well as the GRADEpro Guideline Development Tool [Software]. McMaster University, (developed by Evidence Prime, Inc.), Ontario, Canada.[41,42]

This evaluation will be performed independently by 2 overview authors (ZTSA and GSSC) to assess the quality of evidence throughout the studies for each important outcome. Any disagreements will be resolved through discussion in the overview authors team. The results will be represented in the "Summary of findings" Table 4.

2.4.4. Overview review table. The results reported in the included reviews will be summarized in an "Overview reviews" table by result and then by comparison. The table should include beneficial and detrimental results, frequency or severity of these outcomes in the control groups, estimates of relative and absolute

Table 1

Characteristics of included reviews.

Autor and Year	Data assessed as up to date	Population	Intervention	Comparision interventions	Outcomes for which data werw reported	Meta-analysis	Review limtations

Table 2

Methodological quality assessment of included reviews using AMSTAR-2.

AMSTAR item	Author
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AMSTAR-2 = Assessment of Multiple Systematic Reviews-2.

Table 3

ROBIS assessment.

Review	Trial eligibility criteria	Identification and selection of trials	Data collection and study appraisal	Synthesis and findings	Interpretation

ROBIS = risk of bias in systematic reviews.

Table 4

Summary of findings from included reviews.

Pulmonary Rehabilitation for People with Chronic Obstructive Pulmonary Disease							
Outcome	**Intervention and Comparison intervention**	**Illustrative comparative risks(95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
		Assumed risk	**Corresponding risk**				
		With comparator	**With intervention**				
Outcome #1							
	Intervention/ Comparison #1						
	Intervention/ Comparison #2						
	Etc.....						
Outcome #2							
	Intervention/ Comparison #1						
	Intervention/ Comparison #2						
	Etc.....						
Outcome #3							
	Intervention/ Comparison #1						
	Intervention/ Comparison #2						
	Etc.....						
Outcome #4							
	Intervention/ Comparison #1						
	Intervention/ Comparison #2						
	Etc.....						
Outcome #5							
	Intervention/ Comparison #1						
	Intervention/ Comparison #2						
	Etc.....						
Outcome #6							
	Intervention/ Comparison #1						
	Intervention/ Comparison #2						
	Etc.....						

CI = confidence interval.

effects of interventions, bias risk indications (which may vary by outcome and comparison), and comments if necessary.

2.4.5. Measures of the treatment effect. The main conclusions about the effects of the interventions studied in the included reviews will be summarized and organized around clinically significant categories (e.g., types of interventions or types of outcomes). For this, the results of included studies will be interpreted by the reports made in the reviews, without having to resort to the original data of the study. If the data are reported as a mean difference (MDs) or as an absolute or relative change score, appropriate scales (when possible) will be considered to determine if this was clinically significant. For data presented as standardized mean difference (SMD), with or without 95% confidence intervals (CI) or level of significance (*P* value), Cohen interpretation[43] will be useful to define the effect size. For example, using SMD, the effect size will be classified as small (SMD 0.2–0.5), moderate (SMD 0.5–0.8), or large (SMD >0.8).

2.4.6. Problems in the analysis unit. It is hoped that Cochrane reviews have already addressed these issues. However, if not, it will be considered to contact the original authors for clarification on unit analysis issues that were not reported in the intervention review.

2.4.7. Dealing with lost data. Data from missed outcomes of intervention reviews are either because the review authors did not report on these or found no evidence will be considered as "no evidence." The data from the original test reports will not be extracted if this data has not been collected in the intervention reviews.

2.5. Synthesis of data

The unit of analysis for this overview are systematic reviews (not individual trials). Thus, the PICO elements will be tabulated at the revision level. Results tables will include effect estimates, with 95% confidence intervals (CIs), and measures of heterogeneity/ risk of bias, as appropriate. Estimates of effect of included systematic reviews, categorized by intervention and primary and secondary outcomes, will be extracted and presented in tables and figures. The narrative descriptions of the estimates of the effects of the included revisions will be structured according to the risk of systematic review bias and GRADE evaluation.

Choosing the effect estimate for summary and tabulation will depend on the results reported in several revisions. We intend to standardize the reported results if a result is expressed differently between reviews. We will standardize risk indices (RRs) or odds ratios (ORs) for dichotomous outcomes. We will standardize as differences (MDs) or differences of standardized means (SMDs) using equations published in the Cochrane Handbook for Systematic Reviews of Interventions for continuous results.[40]

The exact method chosen for graphical display will depend on the number of studies available for each specific result. Review Manager *5*[37] will be used to generate standardized effect charts and use them to graphically present the results, with each revision representing a line in the forest plot.

We will discuss the limitations of currently available evidence regarding heterogeneity of inclusion criteria for each review, consistency of effect size for each intervention, and consistent use of outcome measures. We will identify gaps in the current evidence base and make recommendations for future research.

Although the sequence of tables has been planned we know that it depends on the availability and how the effect estimates will be presented by the included reviews.

2.5.1. Subgroup analysis and investigation of heterogeneity. If possible, a subgroup analysis of separate review data will be performed, grouped by differences in the scope of the review. Such as disease severity (stable vs exacerbation); age, and location where pulmonary rehabilitation was offered (hospital, rehabilitation center, home).

3. Ethics and dissemination

Ethical approvals and patient consent are not required, as this overview will be based on a published systematic review. No primary data will be collected. The article in this overview will be submitted for publication in a peer-reviewed journal. The results will also be included in a doctoral thesis and published in scientific conferences.

Author contributions

Conceptualization: Zenia Trindade de Souto Araujo, Brenda Nazare Gomes Andriolo, Patricia Angelica Miranda Silva Nogueira.
Data curation: Zenia Trindade de Souto Araujo.
Formal analysis: Zenia Trindade de Souto Araujo, Gabriela Suellen da Silva Chaves.
Investigation: Zenia Trindade de Souto Araujo, Patricia Angelica Miranda Silva Nogueira.
Methodology: Zenia Trindade de Souto Araujo, Karla Morganna Pereira Pinto Mendonça, Tacito Zaildo Morais Santos, Gabriela Suellen da Silva Chaves.
Project administration: Zenia Trindade de Souto Araujo, Patricia Angelica Miranda Silva Nogueira.
Resources: Zenia Trindade de Souto Araujo, Tacito Zaildo Morais Santos, Patricia Angelica Miranda Silva Nogueira.
Software: Zenia Trindade de Souto Araujo, Gabriela Suellen da Silva Chaves.
Supervision: Karla Morganna Pereira Pinto Mendonça, Patricia Angelica Miranda Silva Nogueira.
Validation: Karla Morganna Pereira Pinto Mendonça, Bruma Morganna Mendonça Souza, Brenda Nazare Gomes Andriolo, Patricia Angelica Miranda Silva Nogueira.
Visualization: Karla Morganna Pereira Pinto Mendonça, Brenda Nazare Gomes Andriolo, Patricia Angelica Miranda Silva Nogueira.
Writing – original draft: Zenia Trindade de Souto Araujo, Karla Morganna Pereira Pinto Mendonça, Bruma Morganna Mendonça Souza, Tacito Zaildo Morais Santos, Gabriela Suellen da Silva Chaves, Brenda Nazare Gomes Andriolo, Patricia Angelica Miranda Silva Nogueira.
Writing – review & editing: Zenia Trindade de Souto Araujo, Karla Morganna Pereira Pinto Mendonça, Bruma Morganna Mendonça Souza, Tacito Zaildo Morais Santos, Gabriela Suellen da Silva Chaves, Brenda Nazare Gomes Andriolo, Patricia Angelica Miranda Silva Nogueira.

Karla Morganna Pereira Pinto de Mendonça orcid: 0000-0001-5734-3707.
Bruma Morganna Mendonça de Souza orcid: 0000-0002-9766-8255.
Tácito Zaildo de Morais orcid: 0000-0002-9495-7078.

Gabriela Suellen da Silva Chaves orcid: 0000-0002-7737-8015.
Brenda Nazare Gomes Andriolo orcid: 0000-0001-6343-666X.
Patrícia Angélica de Miranda Silva Nogueira orcid: 0000-0002-3763-2410.
Zenia Trindade de Souto Araujo orcid: 0000-0003-3447-6990.

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