REVIEW
COPD

Effect of "add-on" interventions on exercise training in individuals with COPD: a systematic review

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ABSTRACT The aim of this review was to identify the effectiveness of therapies added on to conventional exercise training to maximise exercise capacity in patients with chronic obstructive pulmonary disease (COPD).

Electronic databases were searched, identifying trials comparing exercise training with exercise training plus "add-on" therapy. Outcomes included peak oxygen uptake ($V'O_2peak$), work rate and incremental/endurance cycle and field walking tests. Individual trial effects on exercise capacity were extracted and collated into eight subgroups and pooled for meta-analysis. Sensitivity analyses were conducted to explore the stability of effect estimates across studies employing patient-centred designs and those deemed to be of "high" quality (PEDro score >5 out of 10).

74 studies (2506 subjects) met review inclusion criteria. Interventions spanned a broad scope of clinical practice and were most commonly evaluated *via* the 6-min walking distance and $V'O_2peak$. Meta-analysis revealed few clinically relevant and statistically significant benefits of "add-on" therapies on exercise performance compared with exercise training. Benefits favouring "add-on" therapies were observed across six different interventions (additional exercise training, noninvasive ventilation, bronchodilator therapy, growth hormone, vitamin D and nutritional supplementation). The sensitivity analyses included considerably fewer studies, but revealed minimal differences to the primary analysis.

The lack of systematic benefits of "add-on" interventions is a probable reflection of methodological limitations, such as "one size fits all" eligibility criteria, that are inherent in many of the included studies of "add-on" therapies. Future clarification regarding the exact value of such therapies may only arise from adequately powered, multicentre clinical trials of tailored interventions for carefully selected COPD patient subgroups defined according to distinct clinical phenotypes.

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Add-on modalities show mostly minimal additional benefits to exercise capacity after conventional training in COPD http://ow.ly/XABi4

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Introduction

Pulmonary rehabilitation is a highly effective treatment for individuals with chronic obstructive pulmonary disease (COPD), and is associated with significant improvement in quality of life, healthcare utilisation and exercise capacity [1–3]. Benefits of exercise training include improvements in oxygen uptake and endurance time [4], reduced symptoms [1] and muscle composition adaptations such as increased capillary/fibre ratio [5] and increased oxidative capacity [6]. In recent years, significant attention has been directed towards improving the already beneficial effects of pulmonary rehabilitation *via* application of additional ("add-on") therapies on top of conventional exercise training. This is probably due to the emergence of newer therapies (such as pharmacological medicines), new exercise modalities and more readily available equipment (such as portable noninvasive ventilation (NIV) units). The effectiveness of such supplemental therapies, however, is unclear.

The only existing systematic review of such therapies was conducted over a decade ago [7]. Due to significant methodological limitations and small study sample sizes, the authors concluded there was insufficient evidence to estimate the value of most supplemental interventions except supplemental oxygen (which demonstrated a clear lack of benefit). The increased number of studies conducted since this review, however, offers greater potential to better estimate the usefulness of "add-on" therapy to exercise training. It is also crucial that the effects of interventions seeking to boost training responses are rigorously determined according to a robust range of end-points specific to the physiological adaptations of exercise in this patient group. This is likely to improve our understanding of the mechanisms explaining their role in exercise training, and potentially enhance their translation into clinical practice. If no further clarification is able to be determined regarding the value of "add-on" therapies to exercise training in patients with COPD, one must question the scientific approach to clinical research in this area and consider how best to address any emergent shortcomings in order to improve future studies and, ultimately, clinical patient care.

The principal aim of this review was to determine whether "add-on" therapies, applied in conjunction with conventional exercise training in pulmonary rehabilitation, improve exercise capacity in individuals with COPD more than conventional exercise training alone. The secondary aim was to examine the effectiveness of "add-on" therapies specifically in studies that adopted highly specific, patient-centred approaches to the study design. As pulmonary rehabilitation benefits are driven largely by physiological adaptation of skeletal muscles in response to exercise training, we focused on a comprehensive range of outcomes specifically related to exercise capacity.

Methods

Study selection criteria

Randomised and quasi-randomised controlled clinical trials were eligible for inclusion if they compared exercise training (comprising aerobic (lower limb endurance) training) with exercise training plus at least one additional treatment modality (no exclusions) in patients with COPD (defined by study authors). Studies were considered quasi randomised if participants were assigned to interventions by methods such as sequential allocation, date of birth, *etc*. In line with the clear physiological mechanisms underpinning exercise training effects in COPD, studies were only included in the review if they reported data from at least one of the following exercise capacity outcomes: peak oxygen uptake ($V'O_2peak$; metabolic equivalents), peak work rate (watts), cycle endurance test (time), incremental shuttle walk test (ISWT; distance, time), endurance shuttle walk test (ESWT; time, distance), 6-min walk test (6MWT; distance) and 12-min walk test (12MWT; distance). Outcomes such as quality of life or symptoms were not considered for this review.

Search strategy

Six databases (CENTRAL, MEDLINE, EMBASE, SciELO, PEDro and CINAHL) were searched in April 2014 without limits using the following subject headings (no free text terms): (COPD OR chronic obstructive pulmonary disease) AND (randomised OR randomized) AND (exercis* OR exercise training OR aerobic exercise training). Differences between database subject heading structures (*e.g.* MeSH *versus* Emtree) resulted in differences between some search terms across platforms. No hand searching of conference proceedings was undertaken. Search yields were exported to Reference Manager v12 (Thomson Reuters, Philadelphia, PA, USA) and duplicates discarded. Studies were scrutinised on title and abstract by two independent reviewers (C.A. Camillo and H. van Remoortel) and coded as either "include", "exclude" or "awaiting full text". Disagreements were resolved by an independent, third reviewer (C.R. Osadnik). Eligibility criteria were applied by two study investigators and further hand searching performed by examination of reference lists of included studies and comparison with the earlier systematic review [7]. Studies that included more than one relevant "add-on" therapy type (*e.g.* pulmonary rehabilitation *versus* pulmonary rehabilitation plus oxygen *versus* pulmonary rehabilitation plus nutrition) were included but represented once in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Data extraction and quality appraisal

Data were extracted into an electronic spreadsheet using a standardised template. Study quality was assessed using the PEDro scale. This validated scale [8] rates internal and external validity according to 11 criteria, appraised according to standardised decision rules, to derive a total quality score out of 10 (higher=better; first item not quantified). No studies were excluded on the basis of quality. Where data were missing or unclear, attempts were made to contact authors *via* email. Study characteristics and quality were summarised and presented in tables.

Analysis

Data were pooled for meta-analysis in Review Manager v5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) according to eight clinically homogenous intervention groups. These were: 1) additional exercise training modalities, with subgroups for lower limb strength training, upper and lower limb strength training and other; 2) NIV; 3) oxygen; 4) heliox; 5) prescription medications, with subgroups for tiotropium, anabolic steroids, growth hormone, vitamin D and hypertonic saline; 6) nutrition, with subcategories for proteins/fats, creatine and amino acids; 7) breathing exercises, with subgroups of inspiratory muscle training and breathing retraining; and 8) other. A complete list of interventions included within each group classification is provided in table 1. Data were entered as change from baseline values wherever possible. If change data were unable to be obtained (from the article or author contact), end-point (post-intervention) data were included in the meta-analysis in accordance with Cochrane guidelines [83].

Data were combined on an outcome-by-outcome basis using weighted mean differences of native metrics (*e.g.* metres, $L{\cdot}min^{-1}$, *etc.*) with a fixed effect model wherever possible. Standardised mean differences were used to pool data for outcomes containing multiple measurement types (*e.g.* walk test time and distance). A random effects model was used where statistical heterogeneity was "greater than moderate", indicated by an I^2 statistic >60% and Chi-squared $p<0.05$. For studies that involved multiple "add-on" interventions, participant numbers in the control group were evenly divided for analysis according to the number of interventions, in order to derive accurate effect estimates and avoid data duplicity [83]. Data were not weighted or pooled across different intervention groups due to clinical heterogeneity regarding their application. Data were summarised in a meta-analysis matrix, with each cell representing the result of the pooled analysis result for a given intervention (row) on a given outcome (column). Data from individual studies may therefore appear more than once across columns. A representative forest plot was generated for the most commonly reported outcome (6MWT). The secondary aim of the study was addressed *via* meta-analysis of data originating only from studies that used highly specific eligibility criteria deemed well suited to the "add-on" intervention, in accordance with a patient-centred care model.

Sensitivity analyses

One sensitivity analysis was defined *a priori* and performed to determine the impact of studies identified as quasi randomised on effect estimates. A *post hoc* analysis was also undertaken to explore the impact of removing studies deemed to be low quality (PEDro score $\leqslant 5$) from the principal analysis. For both analyses, relevant studies were removed from the principal meta-analysis and findings compared between the original and subsequent analyses.

Results

From 2524 records identified in the database search, 74 studies of 2506 individuals with COPD met eligibility criteria and were included in the review (figure 1). Characteristics of the included studies are presented in table 1 and figure 2.

Three studies [24, 33, 81] reported data from more than one appropriate intervention arm. The methodological quality of the included studies was moderate (median (interquartile range) PEDro score 5 (4–7); table 2), due mainly to lack of intention-to-treat analysis (n=63), therapist blinding (n=55) and allocation concealment (n=54). Significant statistical heterogeneity was only observed in five weighted analyses, namely: nutritional supplementation ($V'O_2$peak I^2=63%), anabolic steroids supplementation ($V'O_2$peak I^2=66%), NIV (cycled endurance time I^2=74%), breathing retraining (12MWT I^2=74%) and growth hormone (6MWT I^2=82%). Inspection of study methodology and participant characteristics of these trials revealed minor differences that were not considered indications for exclusion from analysis. Meta-analysis of these data therefore proceeded with application of a random effects model (table 3). The duration of interventions varied largely, ranging from 10 to 50 sessions (mean±SD 27±19 sessions) and exceptionally reaching 108 sessions (breathing exercises group). Studies typically reported data from one (n=46) or two (n=21) exercise outcomes, most commonly the 6MWT (figure 3) and $V'O_2$peak. The mean rate of attrition from included studies was modest (table 1) but similar across intervention and control groups (11.4% *versus* 9.6%, respectively).

TABLE 1 Description of studies included in the final screening

First author [ref.]	Year	Completed n (% of initial)	Respiratory rehabilitation programme			Exercise test	PEDro score
			Add-on intervention	Components of training	Exercise training sessions n		
Additional exercise modalities							
Benton [9]	2013	19 (100)	Single set of resistance training	Cy, Tr	16	6MWT	4
Vonbank [10]	2012	24 (100)	Strength training	Cy	24	CPET	3
Bernard [11]	1999	36 (80)	Strength training	Cy	36	**CPET**[+]	5
Dourado [12]	2009	24 (73)	Strength training	Tr, Cal	36	6MWT	4
Phillips [13]	2006	19 (unclear)	Strength training	Cy, Tr, Cal, PE	13	6MWT	4
Mador [14]	2004	24 (unclear)	Strength training	Cy, Tr	24	CPET, 6MWT	6
Würtemberger [15]	2001	24 (100)	Strength training	Cy, PE	NR	CPET, 6MWT	4
Alexander [16]	2008	20 (75)	Strength training	Cy, Tr	16	6MWT	3
Holland [17]	2004	38 (100)	Upper and lower limb strength	Cy, Tr	12	6MWT	7
Subin [18]	2010	17 (100)	Upper and lower limb strength	Tr	20	6MWT	4
Sívori [19]	1998	28 (65)	Upper and lower limb strength	Cy	24	CPET, 12MWT	4
Costi [20]	2009	46 (92)	Upper and lower limb strength	Tr, Cal, St	15	**6MWT**[§]	8
Vivodtzev [21][#]	2006	17 (100)	NMES	Tr, Cal, St	16	6MWT	5
Rooyackers [22]	2003	24 (100)	Eccentric cycling	Cy, St	50	CPET, 6MWT	4
Gloeckl [23]	2012	72 (88)	Whole body vibration	Cy, Cal, St, PE, Nut	15	**6MWT**[§,f]	6
NIV							
Johnson [24][¶]	2002	22 (79)	Bi-level NIV	Tr, PE	12	CPET[f]	4
Toledo [25]	2007	18 (100)	Bi-level NIV	Tr	36	CPET	3
Reuveny [26][#]	2005	19 (79)	Bi-level NIV	Tr	16	CPET	6
Costes [27]	2003	14 (100)	Bi-level NIV	Cy	24	CPET, **endurance**[##]	4
van't Hul [28][#]	2006	21 (72)	Inspiratory support	Cy	24	ISWT, endurance	8
Hawkins [29]	2002	19 (66)	Proportional assisted ventilation	Cy	18	CPET, endurance	5
Bianchi [30]	2002	19 (58)	Proportional assisted ventilation	Cy, St, PE, Nut	18	CPET, 6MWT	5
Garrod [31]	2000	37 (82)	Nocturnal NIV	Cy, Tr, St, PE	16	**ISWT**[§,f]	6
Duiverman [32][#]	2008	62 (86)	Nocturnal NIV	Cy, Tr, St, IMT, PE, Nut	36, plus 69 nights of NIV	6MWT, endurance, CPET	4
Oxygen							
Scorsone [33][¶]	2010	30 (100)	Supplementary oxygen	Cy	24	CPET, endurance[f]	5
Emtner [34][#]	2003	29 (100)	Supplementary oxygen	Cy, PE	21	CPET, endurance	7
Garrod [35][#]	2000	22 (88)	Supplementary oxygen	Cy, Tr, Cal, PE	18	ISWT	8
Wadell [36][#]	2001	20 (100)	Supplementary oxygen	Tr	24	6MWT	6
Dyer [37][#]	2012	47 (85)	Supplementary oxygen	Tr, St, PE	14	**ESWT**[§,f]	6
Rooyackers [38][#]	1997	24 (unclear)	Supplementary oxygen	Cy, Cal, St, PE	50	CPET, 6MWT	5
Bjørgen [39]	2009	12 (79)	Supplementary oxygen	Cy	24	CPET[f]	3
Ringbaek [40][#]	2013	38 (84)	Continuous oxygen supplement	Cy, Tr, PE	14	ESWT[f]	5

Continued

TABLE 1 Continued

First author [ref.]	Year	Completed n (% of initial)	Respiratory rehabilitation programme			Exercise test	PEDro score
			Add-on intervention	Components of training	Exercise training sessions n		
Heliox							
Johnson [24]¶	2002	21 (88)	Supplementary heliox	Tr, PE	12	CPET[f]	4
Eves [41]	2009	31 (82)	Supplementary heliox	Cy, Tr, Cal, St, PE	16	CPET, endurance[f]	9
Scorsone [33]¶	2010	30 (100)	Supplementary heliox	Cy	24	CPET, endurance[f]	5
Prescription medications							
Pasqua [42]#	2010	22 (100)	Tiotropium	Cy, Tr, Cal, IMT	20	6MWT	3
Ambrosino [43]	2008	120 (68)	Tiotropium	Tr	24	6MWT[f]	8
Casaburi [44]	2005	91 (84)	Tiotropium	Tr	24	**Endurance§**	6
Creutzberg [45]	2003	63 (100)	Anabolic steroids	Cy	40	CPET	10
Ferreira [46]#	1998	17 (100)	Anabolic steroids	Cy, IMT	40	CPET, **6MWT##**	7
Miki [47]#	2012	29 (100)	Ghrelin	Cy, Cal, PE	45	6MWT[f]	9
Burdet [48]#	1997	16 (100)	Growth hormone	Aero NR	36	CPET, **6MWT##**	8
Miki [49]#	2013	20 (100)	Ghrelin	Cy, Cal, PE	15	**CPET¶¶**	9
Hornikx [50]	2012	49 (98)	Vitamin D supplement	Cy, Tr, St, PE	36	**CPET¶¶**, 6MWT	8
Blanco [51]#	2013	41 (85)	Sildenafil	Cy, St	36	CPET, endurance[f], 6MWT	8
Satta [52]	1991	20 (unclear)	Ubidecarenone	Tr	NR	CPET	6
Valderramas [53]	2009	64 (94)	Hypertonic saline	Tr, Cal, St	24	**6MWT[f,##]**	8
Nutrition							
Laviolette [54]	2010	20 (92)	Whey protein	Cy, St	24	Endurance	6
Sugawara [55]	2012	26 (83)	MEIN (whey protein)	Tr, Cal, IMT, PE	NR	6MWT	8
Steiner [56]	2003	60 (70)	Carbohydrates, protein and fat	Tr, Cal, PE	14	ISWT[f], ESWT	8
Gurgun [57]#	2013	30 (100)	Carbohydrates, protein and fat	Cy, Tr, St	16	ISWT, 6MWT	4
Broekhuizen [58]	2005	80 (78)	Polyunsaturated fat	Cy, Tr, PE	NR	**CPET+**	7
Deacon [59]	2008	80 (80)	Creatine monohydrate	Cy, Tr, St, PE	21	ISWT[f], ESWT	7
Faager [60]	2006	23 (100)	Creatine monohydrate	Cy, Cal, St, PE	16	ESWT	5
Fuld [61]	2005	25 (66)	Creatine monohydrate	Cy, Cal, St, PE	16	CPET, ISWT[f]	7
Menier [62]	2001	60 (100)	Branched-chain amino acid	Cy, Cal, St	30	CPET	3
Borghi-Silva [63]	2006	16 (unclear)	L-carnitine	Tr, IMT	18	CPET, **6MWT§**	5
Breathing exercises							
Magadle [64]	2007	27 (87)	Inspiratory muscle training	Cy, Tr, St	108	6MWT	7
Mador [65]	2005	29 (76)	Inspiratory muscle training	Cy, Tr, Cal, PE	24	CPET, 6MWT	5
Larson [66]	1999	28 (unclear)	Inspiratory muscle training	Cy	80	CPET	5

Continued

TABLE 1 Continued

First author [ref.]	Year	Completed n (% of initial)	Respiratory rehabilitation programme			Exercise test	PEDro score
			Add-on intervention	Components of training	Exercise training sessions n		
Berry [67]	1996	16 (94)	Inspiratory muscle training	Tr, St	36, plus 96 IMT sessions	CPET, endurance, 12MWT	5
Wanke [68]	1994	42 (unclear)	Inspiratory muscle training	Cy	32, plus 56 IMT sessions	CPET	4
Weiner [69]	1992	24 (unclear)	Inspiratory muscle training	Cy, St	72	Endurance, **12MWT**[§]	5
Dekhuijzen [70][#]	1991	40 (100)	Inspiratory muscle training	Cy, Tr, St	100	CPET, 12MWT	5
Kunikoshita [71]	2006	15 (100)	Inspiratory muscle training	Tr, Cal	18	CPET	4
Sykes [72]	2005	37 (93)	Inspiratory muscle training	Cy, St	40	CPET, 6MWT	7
Goldstein [73]	1989	11 (100)	Inspiratory muscle training	Aero NR	Exercise training[++] plus 40 IMT sessions	Endurance, 6MWT	5
Collins [74]	2008	33 (79)	Ventilation feedback	Cy, Tr	36	CPET, endurance	5
van Gestel [75]	2012	40 (100)	Controlled breathing	Cy, St	10	6MWT	6
Other							
Carrieri-Kohlman [76]	1996	51 (100)	Coaching *versus* monitoring	Tr	12	CPET, 6MWT	5
Zanotti [77]	2012	20 (100)	Osteopathy	Cy, St, PE	20	6MWT	9
Alexander [78]	2012	27 (unclear)	Harmonica playing	Cy, Tr	16	6MWT	4
de Godoy [79]	2003	30 (100)	Psychotherapy	Cy, Tr, Cal, St	24	6MWT	5
Sharifabad [80]	2010	63 (100)	Written disclosure therapy	Cy, Tr, St, PE	24	6MWT	4
Norweg [81][¶]	2005	33 (89)	Activity training/ lectures	Tr, Cal	15, plus ~1 h·week^{-1}	6MWT	3
Deering [82]	2011	41 (100)	Acupuncture	Tr	14	ISWT	6

NIV: noninvasive ventilation; Cy: cycling; Tr: treadmill; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; Cal: calisthenics; PE: psychological or educational support; NR: not reported; 12MWT: 12-min walk test; St: strengthening; NMES: neuromuscular electrical stimulation; Nut: nutritional support; endurance: cycle endurance test; ISWT: incremental shuttle walk test; IMT: inspiratory muscle training; ESWT: endurance shuttle walk test; Aero NR: no aerobic training details reported. [#]: exemplar studies of patient-centred care; [¶]: study included two appropriate interventions; [+]: statistically significant effect favouring intervention for peak work rate outcome; [§]: statistically significant effect favouring intervention; [f]: outcomes with adequate statistical power, according to original publication; [##]: statistically significant effect favouring control; [¶¶]: statistically significant effect favouring intervention for peak oxygen uptake outcome; [++]: training duration of 4 weeks, frequency not reported. Bold indicates statistically significant effects.

Results from the meta-analysis, represented as mean differences weighted according to outcome, are presented in table 3 and figure 3 (6MWT only).

Primary aim

Overall, the meta-analysis revealed few clinically relevant or statistically significant benefits of "add-on" therapy on exercise capacity compared with pulmonary rehabilitation. Significant benefits favouring "add-on" therapy were observed across seven different interventions ("other" additional exercise training, NIV, tiotropium, growth hormone, vitamin D, proteins/fats and amino acids) and five different outcomes (6MWT, $V'O_2$peak, peak work rate, cycle endurance time and ISWT) (table 3, in bold). Most interventions were evaluated across more than one clinical outcome; however, no single intervention category demonstrated statistically significant benefits over multiple outcome measures (*i.e.* within rows, only one significant result in table 3).

Two statistically significant negative effects were observed on exercise capacity, measured by the 6MWT. Both were interventions within the "prescription medications" category. The mean between-group

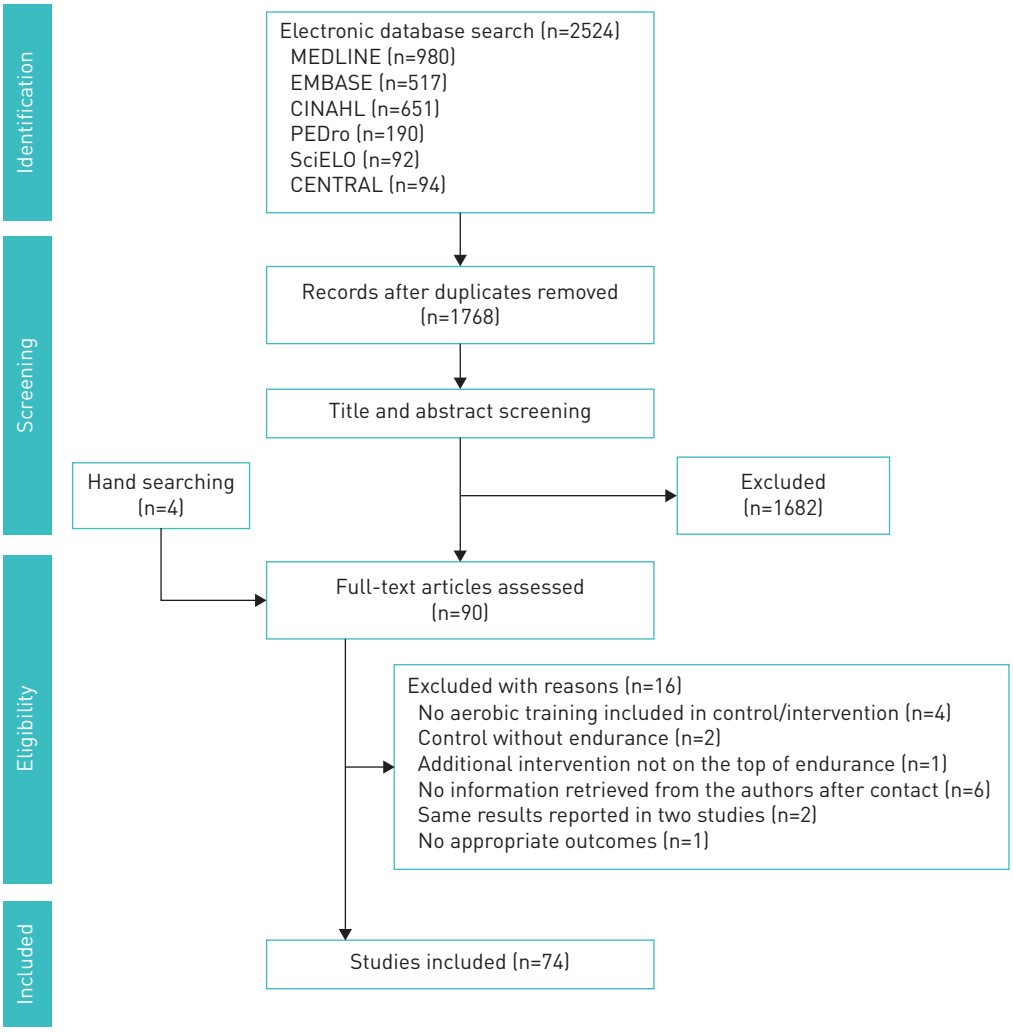

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

difference in 6MWT was −190.0 m (95% CI −247.34–−132.66 m; n=57) for hypertonic saline, and −63.00 m (95% CI −91.09–−34.91 m; n=17) for anabolic steroids.

A *post hoc* pooled meta-analysis of the three "additional exercise training" subcategories revealed an overall statistically significant improvement in 6MWT response (mean difference 18.41 m; 95% CI 9.18–27.63 m; 12 studies of 344 participants).

Secondary aim

18 studies used highly specific eligibility criteria, in accordance with a patient-centred care model (table 1). When considering these data in isolation, loss of statistical significance occurred for many outcomes (table 4). The two remaining significant findings were a positive effect of growth hormone on $V'O_{2peak}$ and a negative

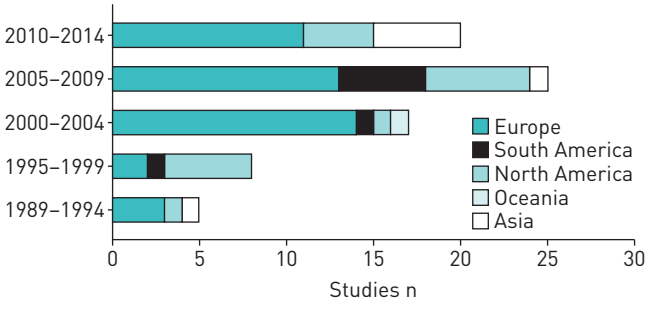

FIGURE 2 Number of studies, according to year and region, which compared exercise training with exercise training plus "add-on" in the present review.

TABLE 2 Overview of methodological quality (PEDro score) of included studies

First author [ref.]	PEDro criteria											
	1#	2	3	4	5	6	7	8	9	10	11	Total
Additional exercise modalities												
Benton [9]	+	+		+						+	+	4
Vonbank [10]		+		+							+	3
Bernard [11]	+	+		+			+			+	+	5
Dourado [12]	+	+		+						+	+	4
Phillips [13]	+	+		+						+	+	4
Mador [14]	+	+	+	+		+				+	+	6
Würtemberger [15]	+	+		+						+	+	4
Alexander [16]		+								+	+	3
Holland [17]	+	+		+			+	+	+	+	+	7
Subin [18]	+	+		+				+			+	4
Sívori [19]	+	+		+						+	+	4
Costi [20]	+	+	+	+			+	+	+	+	+	8
Vivodtzev [21]¶	+	+		+				+		+	+	5
Rooyackers [22]		+		+						+	+	4
Gloeckl [23]		+		+				+	+	+	+	6
NIV												
Johnson [24]§	+	+						+		+	+	4
Toledo [25]	+	+		+						+		3
Reuveny [26]¶		+	+	+			+			+	+	6
Costes [27]				+				+		+	+	4
van 't Hul [28]¶		+	+	+	+		+		+	+	+	8
Hawkins [29]	+	+	+	+						+	+	5
Bianchi [30]	+	+		+					+	+	+	5
Garrod [31]	+	+	+	+				+		+	+	6
Duiverman [32]¶	+	+		+						+	+	4
Oxygen												
Scorsone [33]§		+		+				+		+	+	5
Emtner [34]¶		+		+	+	+		+		+	+	7
Garrod [35]¶	+	+	+	+	+		+	+		+	+	8
Wadell [36]¶	+	+		+	+			+		+	+	6
Dyer [37]¶	+	+		+			+	+		+	+	6
Rooyackers [38]¶	+	+		+				+		+	+	5
Bjørgen [39]	+	+								+	+	3
Ringbaek [40]¶	+	+	+	+						+	+	5
Heliox												
Johnson [24]§	+	+						+		+	+	4
Eves [41]	+	+	+	+	+	+		+	+	+	+	9
Scorsone [33]§		+		+				+		+	+	5
Prescription medications												
Pasqua [42]¶	+	+			+						+	3
Ambrosino [43]	+	+		+	+	+	+		+	+	+	8
Casaburi [44]	+	+		+	+	+				+	+	6
Creutzberg [45]	+	+	+	+	+	+	+	+	+	+	+	10
Ferreira [46]¶	+	+		+	+	+	+			+	+	7
Miki [47]¶	+	+	+	+	+	+	+	+		+	+	9
Burdet [48]¶	+	+		+	+	+	+	+		+	+	8
Miki [49]¶	+	+	+	+	+	+	+	+		+	+	9
Hornikx [50]	+	+		+	+	+	+	+		+	+	8
Blanco [51]¶	+	+		+	+	+	+	+		+	+	8
Satta [52]		+		+	+	+		+			+	6
Valderramas [53]	+	+	+	+	+	+	+	+			+	8
Nutrition												
Laviolette [54]	+	+		+	+			+		+	+	6
Sugawara [55]	+	+	+	+	+	+	+			+	+	8
Steiner [56]	+	+	+	+	+	+	+			+	+	8
Gurgun [57]¶	+	+		+						+	+	4
Broekhuizen [58]	+	+		+	+	+		+		+	+	7
Deacon [59]	+	+		+	+	+	+			+	+	7

Continued

TABLE 2 Continued

First author [ref.]	PEDro criteria											
	1[#]	2	3	4	5	6	7	8	9	10	11	Total
Faager [60]	+	+			+			+		+	+	5
Fuld [61]		+		+	+	+		+		+	+	7
Menier [62]				+				+			+	3
Borghi-Silva [63]		+		+	+					+	+	5
Breathing exercises												
Magadle [64]		+		+	+		+	+		+	+	7
Mador [65]	+	+		+			+			+	+	5
Larson [66]	+	+		+			+			+	+	5
Berry [67]	+	+					+	+		+	+	5
Wanke [68]		+	+							+	+	4
Weiner [69]		+		+				+		+	+	5
Dekhuijzen [70][¶]	+	+		+				+		+	+	5
Kunikoshita [71]		+		+						+	+	4
Sykes [72]	+	+	+	+			+	+		+	+	7
Goldstein [73]		+			+			+		+	+	5
Collins [74]		+		+					+	+	+	5
van Gestel [75]	+	+		+			+	+		+	+	6
Other												
Carrieri-Kohlman [76]	+	+		+				+		+	+	5
Zanotti [77]	+	+	+	+	+		+	+	+	+	+	9
Alexander [78]	+	+	+							+	+	4
de Godoy [79]	+	+		+				+		+	+	5
Sharifabad [80]	+	+		+						+	+	4
Norweg [81][§]	+	+								+	+	3
Deering [82]	+	+		+			+		+	+	+	6

1: eligibility criteria specified; 2: randomisation; 3: concealed allocation; 4: groups similar at baseline; 5: blinding of subjects; 6: blinding of therapists; 7: blinding of assessors; 8: at least one key outcome with >85% of initially allocated subjects; 9: intention-to-treat analysis; 10: between-group statistical comparison; 11: study provides both point measures and measures of variability for at least one key outcome; NIV: noninvasive ventilation; +: criteria decision rule satisfied. [#]: item does not contribute to overall score; [¶]: exemplar studies of patient-centred care; [§]: study included two appropriate interventions.

effect of anabolic steroids on 6MWT. Most findings from this analysis related to data from single and reportedly underpowered studies.

Sensitivity analysis

The removal of quasi-randomised trials (n=2) [27, 62] did not affect any treatment effect estimates. Findings from the principal analysis were also largely unchanged when studies deemed to be of "low" overall quality (PEDro score $\leqslant$5) were removed from the analysis. The only two changes of statistical significance were the loss of benefit of nutrition supplementation (amino acids) on 6MWT due to a lack of available data, and emergence of a large, statistically significant benefit of oxygen therapy on ESWT from one individual study (mean difference 490.00 m; 95% CI 237.90–742.10 m; one study of 47 participants). These data are presented in table 5.

Discussion

This review comprehensively demonstrates that, on average, "add-on" modalities rarely enhance exercise capacity responses to conventional exercise training when applied to a general COPD population. This "evidence of lack of effect" is different from the previous "lack of evidence of effect" observed by Puhan *et al.* [7]. Our findings demonstrate consistency with the recent British Thoracic Society guideline on pulmonary rehabilitation, which yielded minimal supportive evidence-based recommendations regarding the value of select adjunct therapies in pulmonary rehabilitation [84], but expand the scope of findings across a broader range of interventions including different pharmacological interventions and additional exercise training modalities. The latter is particularly important given the high global variation in approaches to exercise training for patients with COPD. The lack of observed benefits in this review does not imply that "add-on" therapies have no role for the management of patients with COPD undertaking exercise training. Statistical significance was rarely observed in our large data synthesis; however, data from some intervention categories (table 3) may provide insight into potentially useful strategies to guide future

TABLE 3 Summary of treatment effect estimates, weighted according to outcome

	V'_{O_2peak} L·min^{-1}	Peak work rate W	Cycle endurance min	ISWT m	ESWT	6MWT m	12MWT m
Additional exercise training							
LL strength	0.10 (−0.08–0.29); N^2=32i *versus* 28c	3.64 (−4.95–12.30); N^4=54i *versus* 54c				2.50 (−20.63–25.64); N^6=62i *versus* 68c	
UL/LL strength	0.00 (−0.18–0.16); N^1=14i *versus* 14c					23.36 (−4.59–51.32)$^{\#}$; N^3=54i *versus* 47c	4.78 (−122.43–131.99); N^1=14i *versus* 14c
Other	0.10 (−0.31–0.51); N^1=12i *versus* 12c	−2.00 (−44.24–42.24); N^1=12i *versus* 12c				**24.43 (0.13–48.74); N^3=57i *versus* 56c**	
NIV	0.08 (−0.08–0.24); N^3=25i *versus* 26c	−0.03 (−7.55–7.50); N^4=35i *versus* 36c	0.61 (−5.23–6.46)$^{\#}$; N^3=27i *versus* 25c	**23.71 (2.65–44.77); N^2=27i *versus* 31c**		−17.35 (−48.39–13.70); N^2=39i *versus* 42c	
Oxygen	−0.11 (−0.29–0.07); N^3=36i *versus* 32c	−1.38 (−5.47–2.72); N^3=36i *versus* 32c	4.70 (−1.96–11.36); N^1=14i *versus* 15c		233.38 (−245.24–712.0) m$^{\#}$; N^2=40i *versus* 45c	−37.0 (−98.61–24.61); N^1=12i *versus* 12c	
Heliox	0.02 (−0.04–0.08); N^2=26i *versus* 20c	4.61 (−0.50–9.72); N^2=26i *versus* 20c	5.20 (−0.17–10.57); N^1=16i *versus* 15c				
Prescription medications							
Tiotropium			**5.35 (0.89–9.81); N^1=47i *versus* 44c**			7.06 (−15.13–29.26); N^2=68i *versus* 74c	
Anabolic steroids	0.10 (−0.02–0.23); N^1=33i *versus* 30c	4.00 (−5.28–13.28); N^1=33i *versus* 30c				**−63.0 (−91.09–−34.91); N^1=10i *versus* 7c**	
Growth hormone	**0.05 (0.01–0.09); N^2=18i *versus* 18c**	−11.00 (−26.48–4.48); N^1=8i *versus* 8c				−26.21 (−148.92–96.50)$^{\#}$; N^2=22i *versus* 23c	
Vitamin D	**0.64 (0.07–1.22); N^1=25i *versus* 24c**	7.00 (−0.28–14.28); N^1=25i *versus* 24c				29.0 (−7.62–65.62); N^1=25i *versus* 24c	
Hypertonic saline						**−190.0 (−247.34–−132.66); N^1=30i *versus* 27c**	
Nutritional supplementation							
Proteins/fats	−0.03 (−0.12–0.06); N^1=38i *versus* 42c	**9.00 (4.32–13.68); N^1=38i *versus* 42c**	2.86 (−2.00–7.72); N^1=10i *versus* 10c	−19.48 (−42.23–3.27); N^2=40i *versus* 50c	−0.24 (−1.65–1.17) min; N^1=15i *versus* 15c	8.02 (−31.21–47.26); N^2=31i *versus* 25c	
Creatine	0.14 (−0.02–0.29); N^1=14i *versus* 11c	4.29 (−9.53–18.11); N^1=14i *versus* 11c		−3.62 (−31.75–24.52); N^2=52i *versus* 53c	−0.11 (−0.46–0.24) units¶; N^3=65i *versus* 63c		
Amino acids		−0.90 (−14.55–12.75); N^1=30i *versus* 30c				**53.00 (24.09–81.91); N^1=8i *versus* 8c**	
Breathing exercises							
Inspiratory muscle training	0.03 (−0.26–0.31) units¶; N^6=97i *versus* 95c	−0.07 (−10.56–10.43); N^4=70i *versus* 69c				12.72 (−16.21–42.26); N^4=55i *versus* 49c	211.45 (−56.66–479.56)$^{\#}$; N^3=39i *versus* 41c
Breathing retraining	0.20 (−1.58–1.98); N^1=17i *versus* 16c		8.50 (−4.38–21.38); N^1=17i *versus* 16c			−12.58 (−35.93–10.77); N^1=20i *versus* 20c	
Other	−0.28 (−0.83–0.27); N^1=24i *versus* 27c			3.20 (−24.06–30.46); N^1=16i *versus* 25c		10.26 (−21.85–42.38); N^6=78i *versus* 183c	

Data are presented as mean difference (95% CI), where the mean difference is the change from baseline and a positive effect estimate favours intervention ("add-on" therapies). Data from individual studies may appear more than once across different outcomes (columns). V'_{O_2peak}: peak oxygen uptake; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; 6MWT: 6-min walk test; 12MWT: 12-min walk test; LL: lower limb; UL: upper limb; NIV: noninvasive ventilation; N^x: number of participants (x is number of studies); i: intervention group; c: control group. $^{\#}$: random effects model; ¶: standardised mean difference. Bold indicates statistically significant treatment effect.

Subgroups and studies	Intervention type	Participants n		Other reported outcomes	Weight %	Mean difference (95% CI)
		Intervention	Control			
Additional exercise training						
Lower limb strength training						
Dourado [12]	Strength training	11	13		21.1	17.00 (−33.35–67.35)
Phillips [13]	Strength training	10	9		16.3	6.10 (−51.22–63.42)
Benton [9]	Single set of resistance training	10	9		17.2	3.50 (−52.27–59.27)
Mador [14]	Strength training	11	13	CPET	5.6	−4.60 (−102.05–92.85)
Würtemberger [15]	Strength training	10	14	CPET	33.8	−5.40 (−45.21–34.41)
Alexander [16]	Strength training	10	10		6.0	−10.05 (−104.79–84.69)
Subtotal (95% CI)		**62**	**68**		**100.0**	**2.50 (−20.63–25.64)**
Upper and lower limb training						
Costi [20]	Upper and lower limb strength	23	23		34.3	50.20 (28.87–71.53)
Subin [18]	Upper and lower limb strength	9	8		38.6	10.40 (−3.68–24.48)
Holland [17]	Upper and lower limb strength	22	16		27.1	7.90 (−24.61–40.41)
Subtotal (95% CI)		**54**	**47**		**100.0**	**23.36 (−4.59–51.32)#**
Other training						
Vivodtzev [21]	Whole body vibration	9	8		6.7	39.00 (−54.57–132.57)
Gloeckl [23]	NMES	36	36		89.1	26.70 (0.94–52.46)
Rooyackers [22]	Eccentric cycling	12	12	CPET	4.2	−47.00 (−165.60–71.60)
Subtotal (95% CI)		**57**	**56**		**100.0**	**24.43 (0.13–48.74)**
NIV						
Duiverman [32]	Nocturnal NIV	30	32	Endurance, CPET	30.0	15.00 (−41.69–71.69)
Bianchi [30]	Proportional assist ventilation	9	10	CPET	70.0	−31.20 (−68.30–5.90)
Subtotal (95% CI)		**39**	**42**		**100.0**	**−17.35 (−48.39–13.70)**
Oxygen supplementation						
Rooyackers [38]	Supplemental oxygen	12	12	CPET	NA	−37.00 (−98.61–24.61)
Prescription medications						
Ambrosino [43]	Tiotropium	57	63		91.1	7.30 (−15.96–30.56)
Pasqua [42]	Tiotropium	11	11		8.9	4.66 (−69.63–78.95)
Subtotal (95% CI)		**68**	**74**		**100.0**	**7.06 (−15.13–29.26)**
Ferreira [46]	Anabolic steroids	10	7	CPET	NA	−63.00 (−91.09– −34.91)
Miki [47]	Growth hormone	14	15		56.3	29.00 (−10.69–68.69)
Burdet [48]	Growth hormone	8	8	CPET	43.7	−97.21 (−193.28– −1.14)
Subtotal (95% CI)		**22**	**23**		**100.0**	**−26.21 (−148.92–96.50)#**
Hornikx [50]	Vitamin D supplementation	25	24	CPET¶	NA	29.00 (−7.62–65.62)
Valderramas [53]	Hypertonic saline	30	27		NA	−190.00 (−247.34– −132.66)
Nutritional supplementation						
Sugawara [55]	MEIN (whey protein)	16	10		3.7	82.70 (−38.59–203.99)
Borghi-Silva [63]	L-carnitine	8	8	CPET	64.8	53.00 (24.09–81.91)
Gurgun [57]	Carbohydrates, protein and fat	15	15	ISWT	31.5	−0.70 (−42.16–40.76)
Subtotal (95% CI)		**39**	**33**		**100.0**	**37.17 (13.89–60.44)**
Breathing exercises						
Inspiratory muscle training						
Sykes [72]	Inspiratory muscle training	20	17	CPET	38.3	35.40 (−12.33–83.13)
Magadle [64]	Inspiratory muscle training	14	13		18.6	17.90 (−50.58–86.38)
Goldstein [73]	Inspiratory muscle training	6	5	Endurance	28.1	−4.00 (−59.74–51.74)
Mador [65]	Inspiratory muscle training	15	14	CPET	15.0	−20.20 (−96.36–55.96)
Subtotal (95% CI)		**55**	**49**		**100.0**	**12.72 (−16.81–42.26)**
Breathing retraining						
van Gestel [75]	Controlled breathing	20	20		NA	−12.58 (−35.93–10.77)
Other						
Zanotti [77]	Osteopathy	10	10		17.1	64.80 (−12.94–142.54)
Alexander [78]	Harmonica playing	9	18		4.6	39.24 (−110.32–188.80)
de Godoy [79]	Psychotherapy	14	16		24.5	35.30 (−29.63–100.23)
Norweg [81]	Activity training	11	6		14.5	19.63 (−64.80–104.06)
Norweg [81]	Lectures	10	6		14.2	−17.52 (−102.70–67.66)
Carrieri-Kohlman [76]	Coaching *versus* monitoring	24	27	CPET	25.2	−46.02 (−110.02–17.98)
Subtotal (95% CI)		**78**	**83**		**100.0**	**10.26 (−21.85–42.38)**

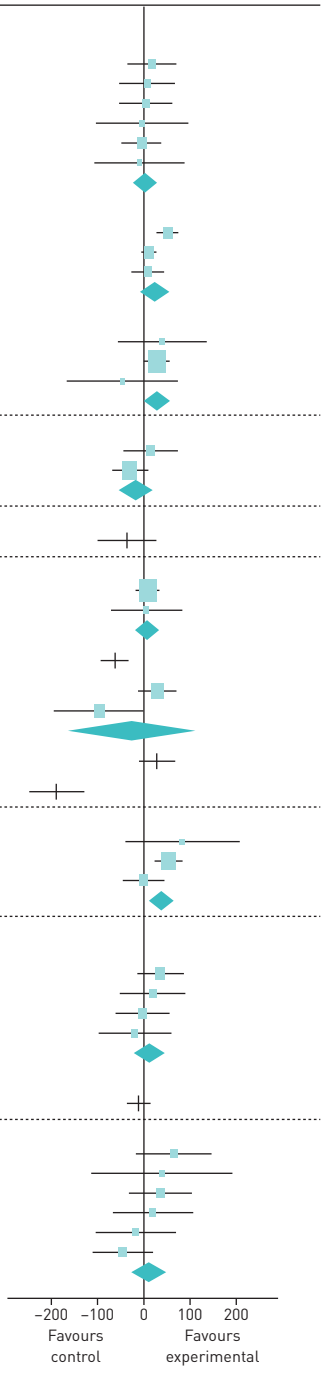

FIGURE 3 Forest plot of the effect of "add-on" therapies on 6-min walking distance change (in metres). Effect estimates (mean differences) without coloured shading denote unweighted analyses of data from single studies within intervention groups or subgroups. CPET: cardiopulmonary cycle exercise test; NMES: neuromuscular electrical stimulation; NIV: noninvasive ventilation; NA: not available; ISWT: incremental shuttle walk test. #: random effects model used for meta-analysis; ¶: statistically significant positive effect reported.

research. For example, the magnitude and direction of effect estimates (although nonsignificant) were consistent across all except one study within the "additional exercise training modalities" category for $V'O_2$peak, peak work rate, 6MWT and 12MWT. The magnitude of estimated mean improvement in 6MWT following both "upper and lower limb strength" and "other" training subcategories was also close to the threshold of the minimally important difference (MID) for this outcome [85, 86]. Further research may therefore be warranted to investigate the potential for additional exercise training modalities to enhance exercise training effects, in more select patient subgroups. Our *post hoc* pooled analysis of the three

TABLE 4 Summary of standardised effect estimates for studies defined as "exemplar" models of patient-centred care

	$V'O_{2peak}$ L·min^{-1}	Peak work rate W	Cycle endurance min	ISWT m	ESWT	6MWT m	12MWT m
Additional exercise training							
LL strength							
UL/LL strength							
Other						39.00 (−54.57–132.57); N^1=9i *versus* 8c	
NIV	0.15 (−0.29–0.59) units¶; N^2=39i *versus* 42c	8.00 (−5.53–21.53); N^1=9i *versus* 10c	3.50 (−1.38–8.38); N^1=10i *versus* 11c	17.00 (−5.47–39.47); N^1=10i *versus* 11c		15.00 (−41.69–71.69); N^1=30i *versus* 32c	
Oxygen		−4.52 (−17.07–8.03); N^2=26i *versus* 27c	4.70 (−1.96–11.36); N^1=14i *versus* 15c		233.38 (−245.24–712.0) m#; N^2=40i *versus* 45c	−37.0 (−98.61–24.61); N^1=12i *versus* 12c	
Heliox							
Prescription medications							
Tiotropium						4.66 (−69.63–78.95); N^1=11i *versus* 11c	
Anabolic steroids	−0.59 (−1.58–0.40) units¶; N^1=10i *versus* 7c					**−63.0 (−91.09– −34.91); N^1=10i *versus* 7c**	
Growth hormone	**0.05 (0.01–0.09); N^2=18i *versus* 18c**					−26.21 (−148.92–96.50)#; N^2=22i *versus* 23c	
Vitamin D							
Hypertonic saline							
Nutritional supplementation							
Proteins/fats				−26.00 (−72.28–20.28); N^1=15i *versus* 15c	−0.12 (−0.84–0.6) units¶; N^1=15i *versus* 15c	−0.70 (−42.16–40.76); N^1=15i *versus* 15c	
Creatine							
Amino acids							
Breathing exercises							
Inspiratory muscle training	−0.06 (−0.19–0.07); N^1=20i *versus* 20c	−7.00 (−32.90–18.90); N^1=20i *versus* 20c					69.00 (−154.89–292.89); N^1=20i *versus* 20c
Breathing retraining							
Other							

Data are presented as mean difference (95% CI), where the mean difference is the change from baseline and a positive effect estimate favours intervention ("add-on" therapies). Data from individual studies may appear more than once across different outcomes (columns). $V'O_{2peak}$: peak oxygen uptake; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; 6MWT: 6-min walk test; 12MWT: 12-min walk test; LL: lower limb; UL: upper limb; NIV: noninvasive ventilation; N^x: number of participants (x is number of studies); i: intervention group; c: control group. #: random effects model; ¶: standardised mean difference. Bold indicates statistically significant treatment effect.

TABLE 5 Sensitivity analysis: summary of treatment effect estimates, weighted according to outcome, including studies with PEDro scores >5 only

	V'_{O_2peak} L·min^{-1}	Peak work rate W	Cycle endurance min	ISWT m	ESWT	6MWT m	12MWT m
Additional exercise training							
LL strength	−0.10 (−0.43–0.23); N^1=11i *versus* 13c	9.00 (−14.60–32.60); N^1=11i *versus* 13c				−4.60 (−102.05–92.85); N^1=11i *versus* 13c	
UL/LL strength						30.90 (−10.39–72.20)$^{\#}$; N^2=45i *versus* 39c	
Other						**26.70 (0.94–52.46); N^1=36i *versus* 36c**	
NIV	0.08 (−0.15–0.32); N^1=9i *versus* 10c	8.00 (−5.53–21.53); N^1=9i *versus* 10c	3.50 (−1.38–8.38); N^1=10i *versus* 11c	**23.71 (2.65–44.77); N^2=27i *versus* 31c**			
Oxygen	−0.04 (−0.26–0.18); N^1=14i *versus* 15c	3.00 (−16.32–22.32); N^1=14i *versus* 15c	4.70 (−1.96–11.36); N^1=14i *versus* 15c		**490.00 (237.90–742.10) m; N^1=24i *versus* 23c**		
Heliox	0.02 (−0.04–0.08); N^2=16i *versus* 15c	4.00 (−4.15–12.15); N^1=16i *versus* 15c	5.20 (−0.17–10.57); N^1=16i *versus* 15c				
Prescription medications							
Tiotropium			**5.35 (0.89–9.81); N^1=47i *versus* 44c**			7.30 (−15.96–30.56); N^1=57i *versus* 63c	
Anabolic steroids	0.10 (−0.02–0.23); N^1=33i *versus* 30c	4.00 (−5.28–13.28); N^1=33i *versus* 30c				**−63.0 (−91.09–−34.91); N^1=10i *versus* 7c**	
Growth hormone	**0.05 (0.01–0.09); N^2=18i *versus* 18c**	−11.00 (−26.48–4.48); N^1=8i *versus* 8c				−26.21 (−148.92–96.50)$^{\#}$; N^2=22i *versus* 23c	
Vitamin D	**0.64 (0.07–1.22); N^1=25i *versus* 24c**	7.00 (−0.28–14.28); N^1=25i *versus* 24c				29.0 (−7.62–65.62); N^1=25i *versus* 24c	
Hypertonic saline						**−190.0 (−247.34–−132.66); N^1=30i *versus* 27c**	
Nutritional supplementation							
Proteins/fats	−0.03 (−0.12–0.06); N^1=38i *versus* 42c	**9.00 (4.32–13.68); N^1=38i *versus* 42c**	2.86 (−2.00–7.72); N^1=10i *versus* 10c	−17.40 (−43.52–8.72); N^1=25i *versus* 35c		82.70 (−38.59–203.99); N^1=16i *versus* 10c	
Creatine	0.14 (−0.02–0.29); N^1=14i *versus* 11c	4.29 (−9.53–18.11); N^1=14i *versus* 11c		−3.62 (−31.75–24.52); N^2=52i *versus* 53c	−0.67 (−2.96–1.63) min; N^2=52i *versus* 53c		
Amino acids							
Breathing exercises							
Inspiratory muscle training	0.48 (−0.17–1.14) units¶; N^1=20i *versus* 17c					29.68 (−9.48–68.84); N^2=34i *versus* 30c	
Breathing retraining						−12.58 (−35.93–10.77); N^1=20i *versus* 20c	
Other				3.20 (−24.06–30.46); N^1=16i *versus* 25c		64.80 (−12.94–142.54); N^1=10i *versus* 10c	

Data are presented as mean difference (95% CI), where the mean difference is the change from baseline and a positive effect estimate favours intervention ("add-on" therapies). Data from individual studies may appear more than once across different outcomes (columns). V'_{O_2peak}: peak oxygen uptake; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; 6MWT: 6-min walk test; 12MWT: 12-min walk test; LL: lower limb; UL: upper limb; NIV: noninvasive ventilation; N^x: number of participants (x is number of studies); i: intervention group; c: control group. $^{\#}$: random effects model; ¶: standardised mean difference. Bold indicates statistically significant treatment effect.

"additional exercise training" subcategories revealed that the upper limit of the confidence interval (27.63 m) was within the range of the MID for the 6MWT. Importantly, the study findings do not detract from the potential clinical benefits of "add-on" therapies on outcomes such as symptoms or quality of life. While improvement in such outcomes is unlikely to be mediated exclusively by extrapulmonary (*e.g.* musculoskeletal) physiological adaptations in response to exercise training, associated alterations in factors such as breathing pattern or subjective control of dyspnoea remain clinically important. Such benefits have been clearly documented in the pulmonary rehabilitation literature [2].

The review also provides evidence from individual studies of negative effects of hypertonic saline and anabolic steroids on 6MWT response, with data from two studies highlighting reductions greatly exceeding the MID [46, 53]. Importantly, supplementation of anabolic steroids is primarily used to enhance muscle strength [87]. While a significant decrease in muscle strength or function would not be an expected consequence of supplementation, it should also not be assumed that exercise capacity would be guaranteed to improve as a result of a pharmacological intervention targeting the cellular genesis of hypertrophic muscle responses. Unless new data emerge, demonstrating opposing findings, the continued use of these interventions in conjunction with standard exercise training in pulmonary rehabilitation appears inadvisable.

The general lack of observed benefit across the breadth of interventions and outcomes could have been affected by three factors. First, as pulmonary rehabilitation comprising exercise training is already a highly effective treatment for patients with COPD [1], further improvements in exercise capacity *via* "add-on" modalities may be challenging to obtain. This is particularly relevant when one considers that pulmonary rehabilitation targets extrapulmonary features of COPD, particularly muscle composition and function, which may have realistic ceilings in terms of the magnitude of expected improvement within a short time-frame. This raises subsequent issues regarding attainable statistical power and sample size estimations for future clinical trials of "add-on" therapies to exercise training in COPD. In such studies, conventional MID thresholds of improvement may not be the most appropriate measure of clinical importance if the underlying exercise training co-intervention is expected to be highly effective for the same outcome. Smaller subsequent levels of improvement (*e.g.* +15 m on top of +30 m 6MWT change) could, for example, be clinically meaningful. Identifying the importance of such additional effects for clinicians and healthcare providers could perhaps be facilitated *via* use of more intuitive research metrics than those commonly seen in the relevant literature. For example, data regarding the "number needed to treat" (the number of patients that need to be treated to have a meaningful impact on one person) were not available in any study included in the review, yet this offers a simple estimate of clinical value in consideration of broader issues such as cost-effectiveness.

Secondly, although the effects of "add-on" therapies on exercise capacity were reported for all interventions included in the review, not all interventions primarily target direct improvements in exercise capacity (*e.g.* psychotherapy or self-management). Interventions such as NIV, for example, aim to ameliorate negative physiological responses to exercise training (such as ventilation limitation) and reduce symptom burden. These indirect influences on exercise training responses may not be fully captured within measures of exercise performance alone. Related to this, the fidelity of interventions must be carefully considered, to ensure they are applied appropriately (*i.e.* to achieve their stated purpose) and deemed adequately acceptable to patients (*i.e.* to ensure adherence). This may have limited the effectiveness of some interventions in this review, such as NIV applied at very low intensities during training. It would be interesting to speculate whether improvement of symptoms during exercise would improve treatment adherence; however, this was not explicitly examined in the present review. These issues highlight the importance of carefully selected outcome reporting in future investigations, and the need for consensus among researchers, clinicians and policy makers to identify the outcomes considered most important to inform clinical practice.

Thirdly, pulmonary rehabilitation studies rarely account for significant disease heterogeneity in COPD. The "one size fits all" model of care applied in most clinical trials seems to derive favourable, clinically important benefits to COPD patients on average; however, further improvements with "add-on" therapies may only be possible in specific patient subgroups. Intuition might suggest the use of highly specific eligibility criteria well suited to "add-on" interventions might be associated with positive results. This was not, however, supported by the findings of our secondary analysis. Interpretation of these exemplar studies was limited by small sample size and low number of studies adopting this approach. This, in itself, is a highly important outcome of the present review that should inform future research. While such patient-centred studies may not yield positive results on exercise capacity, they are likely to confer more accurate information about the true clinical utility of interventions, as they represent the best available estimate of effectiveness in well-defined patient subgroups most likely to derive benefit. Further studies should also strive to achieve adequate statistical power for key outcomes, as small sample sizes and resultant under-powering was a likely contributor to the lack of significant findings observed in this review.

Studies in specific COPD clinical phenotypes are more difficult to conduct, as recruitment is typically slower, with a potential impact upon statistical power. Such studies may confer less external validity than broader studies, but the potential for clinically applicable findings is increased. The development of strong multicentre, international collaborations appears essential in order to conduct high-quality large randomised controlled trials to advance future clinical practice. The diverse organisation of pulmonary rehabilitation programmes across the world [88] can impede such studies; however, standardisation of pulmonary rehabilitation research outcomes, similar to the widespread use of the forced expiratory volume in pharmacological studies, could help overcome this issue. Adoption of "mandatory" outcomes for reporting exercise performance could aid this process, such as the extensive use and importance of the 6MWT documented in recent pulmonary rehabilitation guidelines [85, 89].

Limitations

While pulmonary rehabilitation benefits are well documented on outcomes such as exercise capacity, quality of life and healthcare utilisation [2, 3], the scope of the present review was restricted to outcomes of exercise capacity, admittedly an essential outcome in pulmonary rehabilitation. This was necessary due to the large number of anticipated studies included in the review. The findings therefore relate exclusively to this essential mechanism underpinning exercise training benefits. Potential effects of "add-on" therapies on other important outcomes, such as symptoms or quality of life, should not be extrapolated from our data.

We also included end-point data where changes from baseline data were unavailable. This significantly increased the volume of data and opportunity for meta-analysis to improve findings from the earlier review in this area [7]. A known negative effect of this method, however, is relative overweighting to data from studies contributing change data compared with those contributing end-point data. This is due to the typically narrower confidence intervals around change data compared with end-point data. The consistency of results across clinical trials (figure 3), however, suggests this did not adversely affect the review findings.

The heterogeneous array of interventions and limited opportunity for meta-analysis for some outcomes meant that interpretation of some findings and identification of clinical implications was difficult. Some interventions within the same group have similar goals but work through different mechanisms (*e.g.* neuromuscular electrical stimulation, vibration training and eccentric training to improve muscle function within the "additional training modalities" group). Significant statistical heterogeneity was observed within some outcomes (tables 3 and 4). Despite attempts to maximise opportunities for data pooling, the resultant number of included participants in the meta-analyses was quite low. This was particularly evident in the analysis of carefully selected COPD subgroups (*i.e.* patient-centred studies) and reinforced the difficulty of drawing clinically meaningful conclusions from the large body of literature in this field. Given the observed rate of attrition across studies (table 1), it also seems important that future studies report findings with strict adherence to the principle of intention-to-treat, in order to clarify the true value of treatments applied in the context of "real life" settings. These limitations offer strong support for change in the approach taken towards future investigations in this area. Exercise training represents a complex intervention and standardisation of programme length, intensity and basic outcome reporting would greatly assist the interpretation of future analyses.

Conclusion

Results from our large data synthesis of a diverse array of "add-on" physical, pharmacological, nutritional and behavioural interventions demonstrate minimal clinically important improvements in exercise capacity above those expected from conventional exercise training in pulmonary rehabilitation. This provides a compelling argument discouraging continued attempts to investigate the effectiveness of different "add-on" modalities on exercise capacity using methodologies similar to those included in this review. This does not, however, mean it is unimportant to conduct further studies of "add-on" therapies in this patient group, particularly evaluation of their effect on other outcomes from those covered in this review. Identification of the true value of such therapies may, however, not emerge until studies are carefully designed and implemented in highly selective patient groups using the most appropriate outcomes.

As many pulmonary rehabilitation benefits are driven by physiological change in the peripheral skeletal muscles in response to exercise training, it seems sensible for future clinical trials of interventions in this area to be based upon a strong physiological foundation for specific muscular targets (whether at cellular tissue sites or a physical function level) in select clinical COPD phenotypes. Such interventions should be associated with markers of improvement in relevant outcomes such as exercise capacity and muscle force. Definitive answers regarding the future of pulmonary rehabilitation are therefore only likely to emerge from carefully designed investigations of specific interventions in select patients in larger multicentre studies.

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