Adherence-enhancing interventions for pharmacological and oxygen therapy in patients with COPD: a systematic review and component network meta-analyses

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Adherence to medications is a complex process due to multiple factors. Education, as a stand-alone component, likely improves adherence and quality of life. The effect of other components, including motivation and telemedicine, is unclear. https://bit.ly/4ejeVQ4

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Abstract

Introduction Adherence to COPD management strategies is complex, and it is unclear which intervention may enhance it.

Objectives We aim to evaluate the effectiveness of adherence-enhancing interventions, alone or compared to interventions, for patients with COPD.

Methods This review comprises a component network meta-analysis with a structured narrative synthesis. We searched MEDLINE, Embase, CENTRAL, CINAHL and trial registries on 9 September 2023. We included controlled studies that explored adherence in patients with COPD. Two review authors independently performed the study selection, data extraction and the risk of bias assessment. We involved patients with COPD in developing this systematic review through focus group interviews and displayed the findings in pre-designed logic models.

Results We included 33 studies with 5775 participants. We included 13 studies in the component network meta-analysis that explored adherence. It was mainly assessed through questionnaires. As a continuous outcome, there was a tendency mainly for education (standardised mean difference 1.26, 95% CI 1.13–1.38, very low certainty of evidence) and motivation (mean difference 1.85, 95% CI 1.19–2.50, very low certainty of evidence) to improve adherence. As a dichotomous outcome (*e.g.* adherent/non-adherent), we found a possible benefit with education (odds ratio 4.77, 95% CI 2.25–10.14, low certainty of evidence) but not with the other components. We included six studies that reported quality of life in the component network meta-analysis. Again, we found a benefit of education (mean difference −9.70, 95% CI −10.82– −8.57, low certainty of evidence) but not with the other components.

Conclusions Education may improve adherence and quality of life in COPD patients. Patient focus group interviews indicated that interventions that strengthen patients' self-efficacy and help them to achieve individual goals are the most helpful.

Introduction

COPD management involves a couple of interventions and depends on the stage of the disease [1]. It is mainly based on the use of bronchodilators, corticosteroids and antibiotics. It is crucial that COPD patients adhere to their medications and take them correctly. Adherence to COPD medications reduces the risk of hospital admissions and thus reduces mortality and costs [2]. Conversely, non-adherent patients are more vulnerable to exacerbations and treatment failure [3–5].

The lack of adherence is usually related to the disease itself and the complexity that surrounds it. Patients with COPD may find it challenging to adhere to their medications owing to the complexity of the treatment regimen, adverse effects, poor inhaler technique and mental health comorbidities [6]. Supporting patient adherence is therefore critical to slow disease progression, prevent complications and reduce resource use.

A previous systematic review found that single (*e.g.* education) and multi-component interventions (*e.g.* education and motivation) can improve adherence to pharmacological COPD treatment [7]. However, the results were mainly from single studies and inconclusive regarding which components and component combinations were most effective.

This systematic review aims to evaluate the effectiveness of adherence-enhancing interventions, alone or compared to other adherence-enhancing interventions, for patients with COPD. In addition, we tried to explore which intervention (component) works for which patients and under which circumstances, using methods for synthesising evidence on complex interventions.

Methods

The systematic review was registered on PROSPERO (CRD42022353977) and prepared according to a protocol [8]. The study is reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 [9].

Search strategy and selection criteria

This systematic review consists of a components network meta-analysis (CNMA) with a narrative synthesis of all the included studies.

We searched for all published and unpublished studies without language restrictions regarding adherence-enhancing interventions for COPD on 9 September 2023. A librarian developed the search strategy (appendix 1), two review authors performed the data extraction and consensus was determined through discussion.

We searched MEDLINE, Embase, CENTRAL, CINAHL, trial registries (*e.g.* ClinicalTrials.gov), Epistemonikos and the reference lists of included primary studies and systematic reviews on the same topic for additional references.

We included randomised controlled trials (RCTs) and quasi, cluster and non-randomised controlled studies. Eligible participants were patients with COPD [10].

We included studies that aimed to improve adherence (management, intake or administration) to COPD pharmacological and oxygen therapy.

Our primary outcomes were adherence, health-related quality of life (HRQoL), functional exercise capacity and COPD exacerbations. Our secondary outcomes were hospital admission, mortality, inhaler technique, self-efficacy, COPD knowledge and adverse events [8]. The choice and prioritisation of outcomes were based on clinical judgement and patient views.

We performed two focus group interviews in a COPD self-help group (one before and one after the systematic review) and followed a sequential approach to integrating qualitative and quantitative information. The first interview aimed to understand patients' needs and prioritise the selection of outcomes. The second interview was conducted after the evidence synthesis to present the results to patients. We integrated the patient interview results in logic models and considered them in the interpretation of the results.

Study selection, quality assessment and data extraction

Two review authors, one with clinical expertise and one with methodological expertise, independently performed the study selection. They screened the titles and abstracts of the search results using Rayyan [11]. Subsequently, the same reviewers retrieved the full text of all potentially relevant titles/abstracts and screened them for inclusion while recording the reasons for excluding ineligible studies.

Two review authors used a Microsoft Excel spreadsheet to extract the data independently. Discrepancies were resolved in a discussion until a consensus was reached.

The risk of bias of RCTs was assessed with the Cochrane RoB 2.0 tool [12]. We used the RoB 2 Excel tool to complete the RoB 2 assessment and the Robvis tool to generate traffic light and weighted bar plots [13]. Our effect of interest was starting the intervention.

We used the last available version of RoB 2.0 to assess cluster RCTs [14], the ROBINS-I tool to assess non-randomised studies [15, 16] and the ROB-ME tool to assess missing evidence in the synthesis [17]. In addition to the risk of bias, we assessed the quality of the recruitment strategy [18].

Data analysis

We used odds ratios (ORs) to analyse dichotomous outcomes and the mean difference (MD) or the standardised mean difference (SMD) (to combine different scales) to analyse continuous outcomes.

To determine the degree of complexity, we used the iCAT_SR checklist [19].

We prepared forest plots for all studies [20], performed meta-analyses for studies with sufficient clinical and methodological homogeneity, and explored statistical heterogeneity using prediction intervals or I^2.

We performed two types of meta-analyses to assess the effectiveness of adherence-enhancing interventions (components). First, we ran pairwise random-effects meta-analyses using β-binomial models for meta-analyses of less than five studies and zero event studies [21, 22], with a Bayesian binomial-normal hierarchical model with normal prior for the log-odds ratio with mean 0 and standard deviation 2.82 [23, 24]. Second, we conducted random-effects CNMA to identify the most effective components [20, 25, 26]. In these models, each adherence intervention component (*e.g.* education or reminder) was treated as a separate component (separate node in the network), meaning it had an additive effect. We checked the transitivity assumption.

We performed the analysis with R version 9.4.2.1 (MetaStan, and netmeta; www.r-project.org) and SAS version 9.4 (NLMIXED; SAS Institute, Cary, NC, USA).

We assessed the certainty of the body of evidence for each prioritised outcome with GRADE and prepared summary of findings tables [27]. We also carried out a structured narrative synthesis using tabulations and following GRADE for studies that could not be included in the meta-analyses.

Results

We identified 2753 records from searching literature databases and 1767 records from other sources (figure 1).

Following the screening and the full-text review (253 studies), we included 33 studies (5775 participants), of which two were cluster RCTs [28, 29], one was a quasi-RCT [30] and two were observational studies [31, 32]. Of these 33 studies, 21 contributed data to the meta-analysis.

Characteristics of the included studies

The mean age in the intervention groups ranged from 59.5 to 75.1 years, with around 1821 men and 1088 women. Similarly, the mean age in the control groups ranged from 58.6 to 74.2 years, with around 1829 men and 1108 women. The duration of the intervention ranged from one month to ∼4.7 years.

The intervention consisted of a pharmacist-led intervention in 11 studies [28, 29, 31, 33–40], tele-pharmacy in one intervention [41], a self-management/case management/integrated care programme in six studies [42–47], health coaching in three studies [32, 48, 49], patient education/multi-component educational programme in two studies [50, 51], education and motivational interviewing in two studies [52, 53], telemonitoring/home hospitalisation with a telemedicine programme in two studies [54, 55], robots at home in one study [56], inhaler reminder *via* BreatheMate device in one study [57], a personalised psychological programme in one study [58], cognitive behavioural therapy/information motivation behavioural therapy in two studies [59, 60] and continuous nursing in one study [61]. Adherence was mainly assessed with questionnaires including the Morisky Medication Adherence Scale and Medication Adherence Report Scale.

Among all the included studies, one RCT and one quasi-RCT focused on adherence to oxygen therapy [59, 61]. More details about the included studies are in appendix 2.

Assessment of the intervention complexity

We used the iCAT-SR to assess the intervention complexity (appendix 3). Globally, the assessment of intervention complexity displayed the heterogeneity of complexity within and between the studies. In the

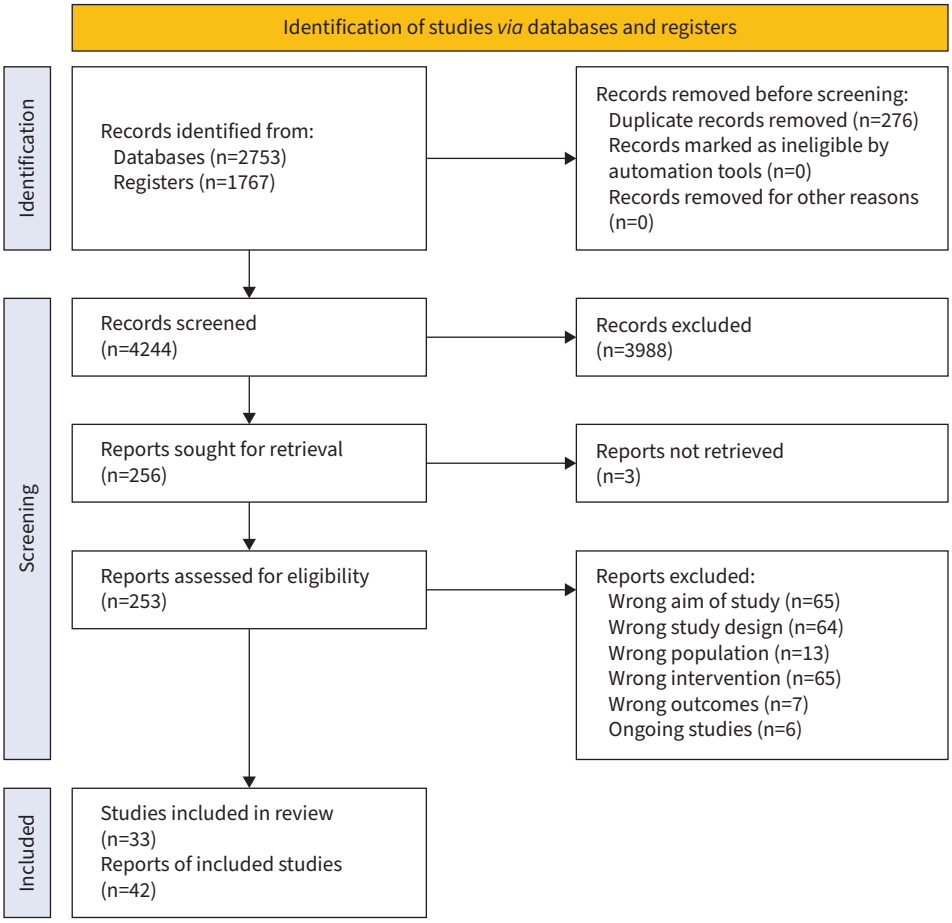

FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.

core dimensions, most of the interventions had more than one component, were multi-target, were directed to a single category of people and the recipient required a basic skill level. There was also high variability in tailoring and the skills required to deliver the intervention. In the optional components, the interventions differed a lot regarding the interaction between intervention components and the dependence of interventions on the setting.

Risk of bias assessment

We report the risk of bias of adherence, HRQoL, COPD exacerbation and hospital admission. Assessment of functional exercise capacity and risk of bias tables and figures are presented in appendix 4.

Adherence

For RCTs, we judged three studies at low risk of bias [33, 45, 59], nine studies at some concern [34, 36, 38, 39, 41, 46, 54, 55, 62] and ten studies at high risk of bias [35, 40, 42, 47, 49, 50, 52, 53, 56, 57]. Most studies that we judged at some concern did not provide sufficient details about allocation concealment, missing data could depend on their true value and selective reporting could not be ruled out because only the journal articles were available (*e.g.* no study protocol or registry entry was available). The issues with high risk of bias studies were concerns regarding intention to treat analysis, missing data were likely to depend on their true value and concerns with selective reporting.

For cluster RCTs, we judged one study at high risk of bias mainly because of issues in recruitment of participants [29]. Another study was judged at some concern because of a lack of details of allocation concealment and missing data [28].

For observational studies [31, 32], we judged both studies at critical risk of bias because they did not consider confounding factors and issues with the classification of the intervention.

Health-related quality of life

For RCTs, we judged three studies at low risk of bias [33, 45, 59], nine studies at some concern [34, 37–39, 42, 44, 55, 58, 62] and eight studies at high risk of bias [35, 40, 43, 47, 48, 53, 56, 57]. Most studies judged at some concern did not provide sufficient details about allocation concealment and only the journal articles were available. Most high risk of bias studies had issues with missing data and serious concerns about the selection of the reported results.

The risk of bias of cluster RCTs [28, 29] and observational studies [31, 32] and the reasons behind our judgement are the same as for adherence.

COPD exacerbations

For RCTs, we judged two studies at low risk of bias [33, 54], three at some concern [34, 38, 55] and four at high risk of bias [35, 42, 48, 53]. The reasons for our judgement are similar to the other outcomes.

Hospital admission

For RCTs, we judged two studies at low risk of bias [33, 54], six studies at some concern [34, 38, 44, 46, 55, 56] and four studies at high risk of bias [35, 40, 42, 48]. The reasons for judging the studies at high risk and some concern are the same as for HRQoL and adherence.

We judged the cluster RCT that reported hospital admission at high risk of bias because of issues in the recruitment of participants [29].

We did not find any issue with the risk of bias due to missing evidence in the synthesis using the RoB-ME tool in the studies included in the network meta-analysis.

Data analysis: component network meta-analysis, pairwise meta-analysis and narrative synthesis

Primary outcomes

Data of the included components in the CNMA are presented in appendix 5.

Adherence

28 studies with 3649 participants reported adherence. We included eight studies that reported adherence as a continuous outcome in the CNMA (figure 2) [32, 36, 39, 41, 53, 54, 56, 63]. Compared to standard care, the overall effect estimate favoured education (SMD 1.26, 95% CI 1.13–1.38), education+motivation (SMD 0.83, 95% CI −1.06–2.72), education+reminder+pulmonary rehabilitation (SMD 0.81, 95% CI −1.05–2.67), education+motivation+telemedicine (SMD 0.54, 95% CI −0.09–1.17), motivation (SMD 1.85, 95% CI 1.19–2.50) and telemedicine (SMD 0.30, 95% CI −0.19–0.79). This was not the case with education+psychosocial support (SMD −0.16, 95% CI −1.30–1.98) and education+motivation+pulmonary rehabilitation (SMD −0.70, 95% CI −0.97– −0.42). The certainty of evidence was very low in all the components.

We included five studies that reported adherence as a dichotomous outcome (*e.g.* adherent/non-adherent) in the CNMA (figure 3) [28, 34, 35, 47, 55]. Compared to standard care, education (OR 4.77, 95% CI 2.25–10.14, low certainty of evidence) resulted in a large increase in adherence. However, the evidence was quite uncertain about education+motivation (OR 1.21, 95% CI 1.02–1.43, very low certainty of evidence) and telemedicine (OR 0.99, 95% CI 0.78–1.25, very low certainty of evidence).

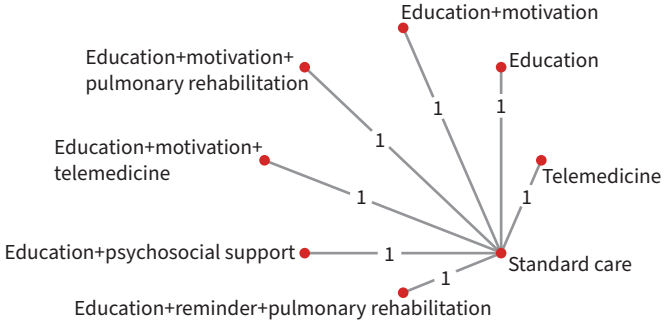

FIGURE 2 Star-shaped component network meta-analysis for adherence (continuous).

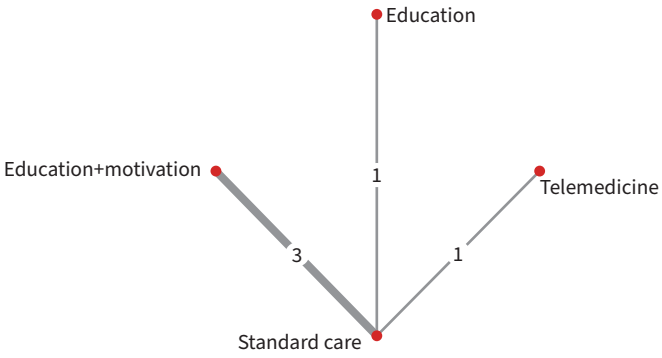

FIGURE 3 Star-shaped component network meta-analysis for adherence (dichotomous).

Overall, authors reported a general improvement in adherence compared to the control group, except for five studies [51, 52, 54, 55, 63].

Health-related quality of life

25 studies with 4216 participants reported HRQoL. We included six studies that reported the total score of the St George's Respiratory Questionnaire (SGRQ) in the CNMA (figure 4) [32, 35, 38, 40, 42, 54]. Based on a minimal clinically important difference (MCID) of −4 units [64] and compared to standard care, the overall effect estimate favoured motivation (MD −13.01, 95% CI −20.83– −5.18), education (MD −9.70, 95% CI −10.82– −8.57) and education+motivation (MD −4.12, 95% CI −7.72– −0.52) as likely to improve the HRQoL (note, higher scores mean stronger reduction in quality of life). However, it was not the case with telemedicine (MD 0.90, 95% CI −3.70–5.50) and education+psychosocial support (MD 1.40, 95% CI −5.79–8.59). The certainty of evidence was very low in all the components except education (low certainty of evidence).

Overall, authors reported an improvement in HRQoL in 14 studies [28, 31, 32, 37–40, 45, 48, 55, 59–61, 63], a limited improvement in two studies [35, 53] and a failure in improvement in ten studies [29, 33, 34, 44, 47, 51, 54, 56–58].

Functional exercise capacity

Three studies reported functional exercise capacity. One study reported a significant improvement [45], while two did not [44, 48].

COPD exacerbations

Eight studies with 1676 participants reported COPD exacerbations. We combined three studies in a pairwise meta-analysis [34, 35, 53], showing a numerical decrease in exacerbations (OR 0.38, 95% CI −0.57–1.17; follow-up 6–12 months) (appendix 6). We did not include the other studies in the meta-analysis because of heterogeneity regarding the statistical measure and follow-up times (appendix 2: characteristics of the outcomes).

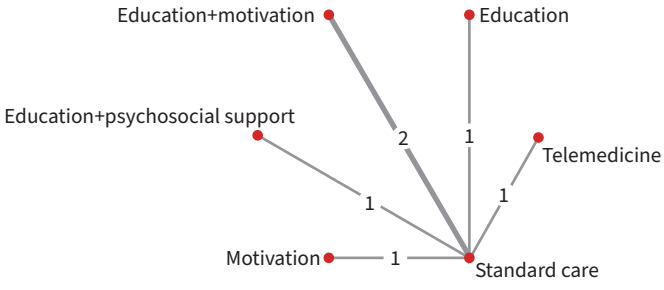

FIGURE 4 Star-shaped component network meta-analysis for health-related quality of life (as assessed by the St George's Respiratory Questionnaire).

Secondary outcomes

Hospital admission

12 studies with 3425 participants reported hospital admission. Six studies reported a decrease in hospital admission [33–35, 38, 40, 46] while six studies did not [29, 44, 48, 54–56].

Four studies with 1662 participants reported mortality [44, 53, 54, 63]. None of the studies reported a decrease in mortality compared to the control groups.

Inhalation technique

Six studies with 1204 participants reported inhalation technique [33, 47, 49–51, 60]. All the studies reported an improvement in inhalation technique compared to the control groups.

Self-efficacy

Six studies with 819 participants reported self-efficacy [32, 48, 51, 54, 58, 61]. Two studies reported an improvement in self-efficacy [32, 61] while four studies did not find a benefit [48, 51, 54, 58].

COPD knowledge

Six studies with 667 participants reported COPD knowledge [34, 35, 45, 47, 53, 54]. Five reported an improvement in COPD knowledge [34, 35, 45, 47, 53] and one study did not find a benefit [54].

Adverse events

None of the included studies reported adverse events.

Assessment of patient recruitment

We had concerns with all the studies except for three RCTs because they did not focus on groups at risk for non-adherence (appendix 7). In the studies that focused on patients at risk for non-adherence, and thus at low concern, one trial included some participants from a rural location with poor social support [56], one included patients with unstable disease [44] and one included participants with low baseline adherence (<80% of expected refills) [41].

Certainty of evidence

Tables 1 to 3 present the summary of findings of the CNMA. Details about the certainty of evidence assessment and the overall synthesis are in appendix 8.

Focus group interviews

Two focus group interviews were held; 14 patients (age 67.7±6.8 years, 71.4% female) participated in the first interview and 10 (age 67.1±8.8 years, 60% female) in the second. We integrated their results into system-based and process-oriented logic models (figures 5 and 6, respectively). Each interview lasted 60–75 min. Our participants explained the factors that might support adherence and burdens for adherent behaviour. The “enhancing” factors were being well informed about the disease, reliable communication with the healthcare professionals, inhalation technique training and physical training. They particularly considered interventions aimed at improving self-efficacy as the most helpful. The main “inhibiting” factors were fear of the consequences of the disease, the lack of information, poor communication with the doctors and bureaucracy. More details about the focus group interviews are in appendix 9.

Applicability assessment

The applicability assessment revealed that most included interventions might be globally applicable (appendix 10). The main limitations are the availability of qualified professionals and costs. The patients pointed out that face-to-face interventions are highly effective and not entirely substitutable by telemedical interventions, and emphasised the importance of considering relevant patient outcomes.

Discussion

This systematic review summarises the available evidence of the effect of adherence-enhancing interventions in COPD patients.

In the CNMA exploring adherence reported as a continuous outcome, we found a positive effect direction for education, motivation and education+motivation. However, the effect estimate of the latter component was smaller than the effect of education and motivation separately. There was also a trend towards an improvement with education+reminder+pulmonary rehabilitation, education+motivation+telemedicine and telemedicine. No benefit was observed with the remaining components. As a dichotomous outcome, we noticed a larger effect with education but not with telemedicine and education+motivation. For the

TABLE 1 Summary of findings: intervention components seeking to improve adherence (outcome adherence reported as continuous outcomes)

Components (*versus* standard care)	SMD (95% CI)	Participants (studies), n	SUCRA (p-value)	Certainty of the evidence (GRADE)	Comments
Education	1.26 (1.13–1.38)	859 (7 RCTs/1 observational)	0.9043	⊕◯◯◯ Very low[¶,+]	Education, as a stand-alone component, may improve adherence compared to standard care but the evidence is very uncertain, based on the Cohen's d effect size[#]
Education+motivation	0.83 (−1.06–2.72)	645 (7 RCTs/1 observational)	0.6720	⊕◯◯◯ Very low[¶,+,§]	The association of education and motivation may improve adherence compared to standard care but the evidence is very uncertain, based on the Cohen's d effect size[#]
Education+reminder +pulmonary rehabilitation	0.81 (−1.05–2.67)	492 (7 RCTs/1 observational)	0.6669	⊕◯◯◯ Very low[¶,+,§]	The association of education, reminder and pulmonary rehabilitation may improve adherence compared to standard care but the evidence is very uncertain, based on the Cohen's d effect size[#]
Education+motivation +telemedicine	0.54 (−0.09–1.17)	516 (7 RCTs/1 observational)	0.6171	⊕◯◯◯ Very low[¶,+,§]	The association of education, motivation and telemedicine may improve adherence compared to standard care but the evidence is very uncertain, based on the Cohen's d effect size[#]
Motivation	1.85 (1.19–2.50)	672 (7 RCTs/1 observational)		⊕◯◯◯ Very low[¶,+,f]	Motivation, as a stand-alone component, may improve adherence compared to standard care but the evidence is very uncertain, based on the Cohen's d effect size[#]
Telemedicine	0.30 (−0.19–0.79)	620 (7 RCTs/1 observational)	0.5040	⊕◯◯◯ Very low[¶,+,f]	Telemedicine, as a stand-alone component, may improve adherence compared to standard care but the evidence is very uncertain, based on the Cohen's d effect size[#]
Standard care		467 (7 RCTs/1 observational)	0.3094		
Education +psychosocial support	−0.16 (−1.30–1.98)	560 (7 RCTs/1 observational)	0.2832	⊕◯◯◯ Very low[¶,+,§]	The association of education and psychosocial support may not improve adherence compared to standard care but the evidence is very uncertain, based on the Cohen's d effect size[#]
Education+motivation +pulmonary rehabilitation	−0.70 (−0.97– −0.42)	583 (7 RCTs/1 observational)	0.0431	⊕◯◯◯ Very low[¶,+,f]	The association of education, motivation and pulmonary rehabilitation may not improve adherence compared to standard care, based on the Cohen's d effect size[#]

Patient or population: COPD; settings: clinical, home and remote; intervention components: education, motivation, reminder, pulmonary rehabilitation, telemedicine, psychosocial support; comparison: standard care; follow-up: range 4–24 months. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group grades of evidence are as follows. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. SMD: standardised mean difference; SUCRA: surface under the cumulative ranking; RCT: randomised controlled trial. [#]: small effect 0.2, medium effect 0.5, large effect ⩾0.8; [¶]: downgraded by two levels for risk of bias because all the evidence is from studies at high risk of bias and some concern, and no study is at low risk of bias; [+]: downgraded by one level for inconsistency because of some variations in the direction of the effects; [§]: downgraded by two levels for imprecision because of the large confidence interval and the small sample size; [f]: downgraded by one level for imprecision because of the small sample size.

HRQoL, and in the CNMA of the SGRQ (total score), we noticed a large benefit of motivation and education as separate components. Similarly to adherence, the potential benefit of combining education and motivation was again less than the individual effect of education and motivation. This may be because there are usually some patients in the population who benefit from education or motivation only, and thus, the number of remaining patients who require both for increasing adherence (*i.e.* more adherence components) is small. Another explanation could be that patients who only received education also became more motivated; adding motivation may not lead to a higher benefit beyond what education alone offers. The overall effect estimate also favoured education+reminder+pulmonary rehabilitation and education+motivation+telemedicine. We combined three studies that reported COPD exacerbations in a

TABLE 2 Summary of findings for intervention components seeking to improve adherence (outcome adherence reported as dichotomous)

Components (*versus* standard care)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Participants (studies), n	SUCRA (p-value)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with components[#]					
Education	428 per 1000	781 per 1000 (628–884)	OR 4.77 (2.25–10.14)	528 (5 RCTs)	0.9999	⊕⊕◯◯ Low[¶,+,§]	Education, as a stand-alone component, may result in a large increase in adherence compared to standard care, based on an MCID of 50 per 100
Education +motivation	428 per 1000	475 per 1000 (433–517)	OR 1.21 (1.02–1.43)	538 (5 RCTs)	0.6339	⊕◯◯◯ Very low[¶,+,f]	The association of education and motivation may not improve adherence compared to standard care but the evidence is very uncertain, based on an MCID of 50 per 100
Telemedicine	428 per 1000	426 per 1000 (369–483)	OR 0.99 (0.78–1.25)	432 (5 RCTs)	0.1850	⊕◯◯◯ Very low[¶,+]	Telemedicine, as a stand-alone component, may not improve adherence compared to standard care but the evidence is very uncertain, based on an MCID of 50 per 100
Standard care				383 (5 RCTs)	0.1812		

Patient or population: COPD; settings: clinical (inpatient and outpatient) and community pharmacies; intervention components: education, motivation, telemedicine; comparison: standard care; follow-up: range 6–12 months. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group grades of evidence are as follows. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. SUCRA: surface under the cumulative ranking; OR: odds ratio; RCT: randomised controlled trial; MCID: minimal clinically important difference. [#]: the risk with components (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI), but it is based on the risk of the corresponding component; [¶]: downgraded by two levels for risk of bias because all the evidence is from studies at high risk of bias and some concern, and no study is at low risk of bias; [+]: downgraded by one level for inconsistency because the CIs do not overlap, but the effect estimates are on the same side of the line of no effect; [§]: upgraded by one level because of the large OR; [f]: downgraded by two levels for imprecision because the 95% CI crosses the threshold.

pairwise meta-analysis and found a decrease in these events. The findings of the narrative synthesis were similar to those of adherence and HRQoL. Education alone likely reduces COPD exacerbations (moderate certainty of evidence), but the benefit is still uncertain regarding the remaining components (very low certainty of evidence). Hospital admission was our main secondary outcome and the one we chose to summarise in the narrative synthesis. The evidence was very uncertain in all components (very low certainty of evidence), with a trivial exception regarding telemedicine (low certainty of evidence).

Exploring the components of complex interventions, rather than just the intervention as a whole, may offer several advantages. For example (and in general), it helps us gain a deeper understanding of the underlying mechanism of action of complex interventions [65], identify the component–outcome relationship that helps implement the complex intervention in different settings [66], standardise the components across different settings instead of using the same component [67] and design future complex interventions to make them more efficient [68]. In the context of adherence-enhancing interventions, exploring the components of complex interventions helps us understand which specific components work best to achieve the desired outcome [69]. Our analysis revealed a possible benefit of education and motivation as separate components, but not with studies that combined multiple components. This result was consistent across all the outcomes and summary syntheses.

The findings of our patient interviews also supported our results. The patients believed “simple” and “essential” interventions, like teaching inhaler technique, might help them remain adherent. Self-efficacy and HRQoL were key for adherence. However, they were reluctant towards other “hard to understand” interventions like telemedicine and devices, especially patients not used to technology. These interventions

TABLE 3 Summary of findings table for intervention components seeking to improve the HRQoL reported with the SGRQ (total score)

Components (*versus* standard care)	MD (95% CI)	Participants (studies), n	SUCRA (p-value)	Certainty of the evidence (GRADE)	Comments
Motivation	−13.01 (−20.83– −5.18)	450 (6 RCTs)	0.9533	⊕◯◯ Very low[#,¶,+,§]	Motivation, as a stand-alone component, may improve the HRQoL measured with the SGRQ compared to standard care but the evidence is very uncertain, considering an MCID of −4 units
Education	−9.70 (−10.82– −8.57)	537 (6 RCTs)	0.8405	⊕⊕◯◯ Low[#,¶,+,f]	Education, as a stand-alone component, may result in a large increase in the HRQoL measured with the SGRQ compared to standard care, considering an MCID of −4 units
Education +motivation	−4.12 (−7.72– −0.52)	551 (6 RCTs)	0.5752	⊕◯◯◯ Very low[#,¶,##]	The association of education and motivation may improve the HRQoL measured with the SGRQ compared to standard care but the evidence is very uncertain, considering an MCID of −4 units
Standard care		423 (6 RCTs)	0.2621		
Telemedicine	0.90 (−3.70–5.50)	528 (6 RCTs)	0.1888	⊕◯◯◯ Very low[#,¶,¶¶]	Telemedicine, as a stand-alone component, may not improve the HRQoL measured with the SGRQ compared to standard care but the evidence is very uncertain, considering an MCID of −4 units
Education +psychosocial support	1.40 (−5.79–8.59)	521 (6 RCTs)	0.1801	⊕◯◯◯ Very low[#,¶,++]	The association of education and psychosocial support may not improve the HRQoL measured with the SGRQ compared to standard care but the evidence is very uncertain, considering an MCID of −4 units

Patient or population: COPD; settings: clinical (inpatient and outpatient) and home; intervention components: education, motivation, telemedicine, psychosocial support; comparison: standard care; follow-up: range 6–12 months. The GRADE Working Group grades of evidence are as follows. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. HRQoL: health-related quality of life; SGRQ: St George's Respiratory Questionnaire; MD: mean difference; SUCRA: surface under the cumulative ranking; RCT: randomised controlled trial; MCID: minimal clinically important difference. [#]: downgraded by two levels for risk of bias because all the evidence is from studies at high risk of bias and some concern, and no study is at low risk of bias; [¶]: downgraded by one level for inconsistency because of some variations in the direction of the effects; [+]: upgraded by one level due to the large effect; [§]: downgraded by two levels for imprecision because the 95% CI crosses the thresholds of moderate and large effect (based on an MCID of −4 units); [f]: downgraded by one level for imprecision because of the small sample size (<800 participants, rule of thumb based on the Cohen's small effect size); [##]: downgraded by one level for imprecision because the 95% CI crosses the threshold of small effect (based on an MCID of −4 units); [¶¶]: downgraded by one level for imprecision because the 95% CI crosses the threshold of small harm (based on an MCID of −4 units); [++]: downgraded by two levels for imprecision because the 95% CI crosses the thresholds of small harm and benefit (based on an MCID of −4 units).

were acceptable if they received adequate training. In addition, "simple" interventions have the advantage that they are usually at a lower risk of suffering applicability issues.

Some previous studies compared multi-component with single-component interventions but did not find a benefit of complex interventions. For example, a systematic review investigated the effect of multi-component nutrition education interventions on children's and adolescents' dietary intake-related behaviour and found inconsistent evidence [70]. Another one reported no evidence to support multiple components compared to single-component interventions in changing the behaviour of healthcare professionals [71]. Conversely, a CNMA showed a greater benefit of multi-component interventions in improving adherence in chronic diseases [72].

From our perspective, the lack of evidence of the benefits of multi-component compared to single-component interventions could be understood, although not absolutely. Single components are often easier to understand for patients and may provide a more straightforward message, especially for those with COPD, who are generally over 60 years old. Adding multiple components may dilute the effect and make the patients unable to cope with the intervention. In addition, single-component interventions are typically easier for healthcare providers to implement, because some components, like psychosocial support and telemedicine, require qualified professionals and logistics that are more expensive and may not always be available.

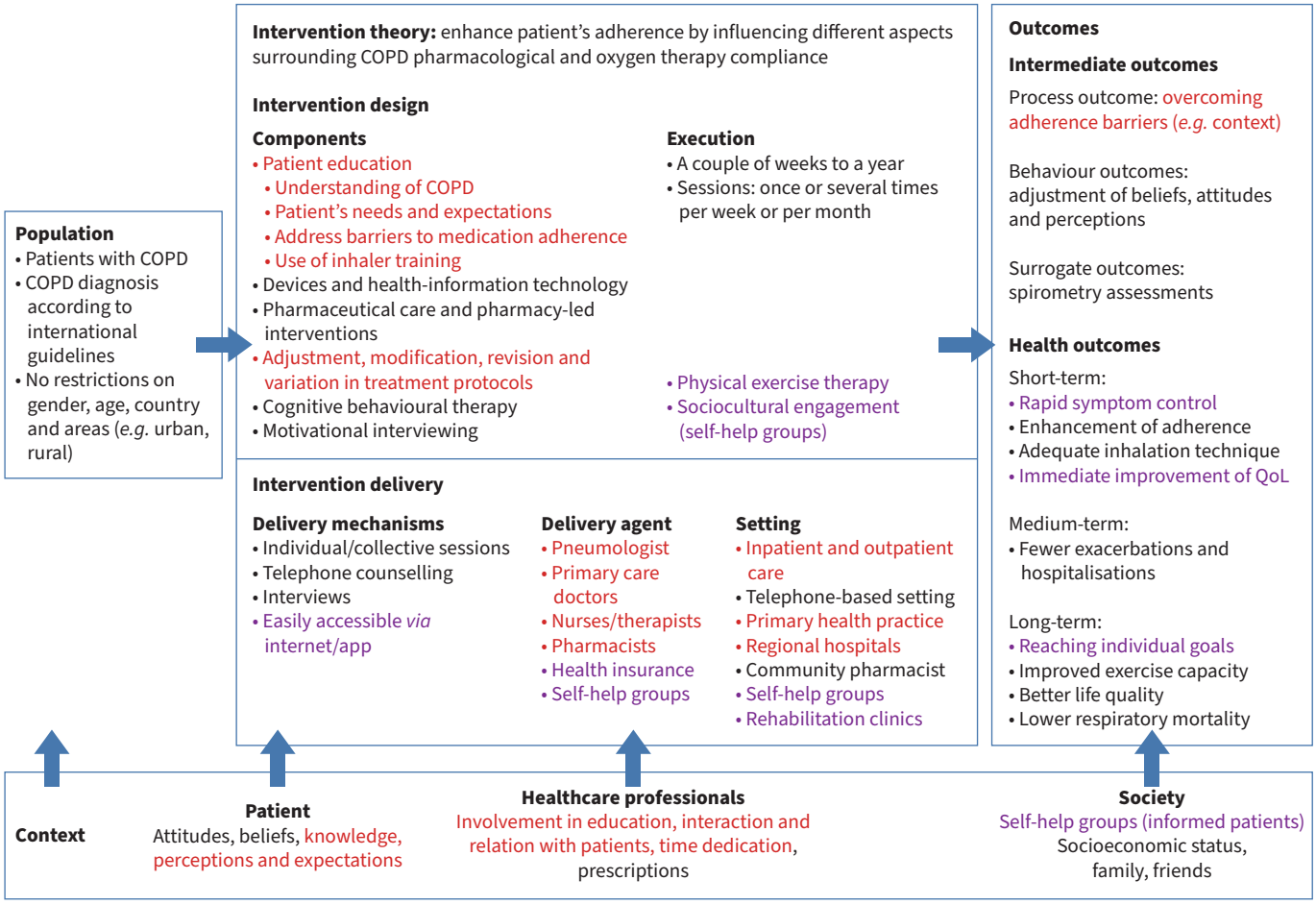

FIGURE 5 System-based logic model supplemented by the patient concept on the topic of therapy adherence. Red text represents areas of patient focus; purple text represents patient suggestions. QoL: quality of life.

We did not find a potential benefit of pulmonary rehabilitation regarding adherence, contrasting with the patients' views about physical activity. This may be explained by the few included studies involving rehabilitation, the focus on exercise training, the lack of specific adherence strategies and individual variabilities.

Our review has some limitations. The principal one is the small number of studies with multiple components. This resulted in downgrading by multiple levels for imprecision and may have caused an overestimation of the effect of single-component interventions (like education and motivation). The categorisation of the components was also not clear-cut because the content of the interventions shared many similarities and studies used different terminologies. Finally, we included interventions that did not focus on adherence but assessed adherence (as an outcome). Thus, the analysis may have underestimated the effect of some components.

Conclusions

This systematic review suggests that education likely improves adherence to COPD treatment. Combining different and adding additional components probably does not increase adherence further. The patients in the focus group interviews emphasised the importance of tailored, simple and face-to-face interventions. They welcomed telemedicine but only when not entirely omitting direct interactions.

Future research should compare different intervention components directly. It may also be valuable to compare single components with multi-component interventions to identify more effective components and assess the additive or synergic effect. The studies should include non-adherent patients or those at risk for non-adherence to avoid ceiling effects. Finally, adherence measurement should be standardised.

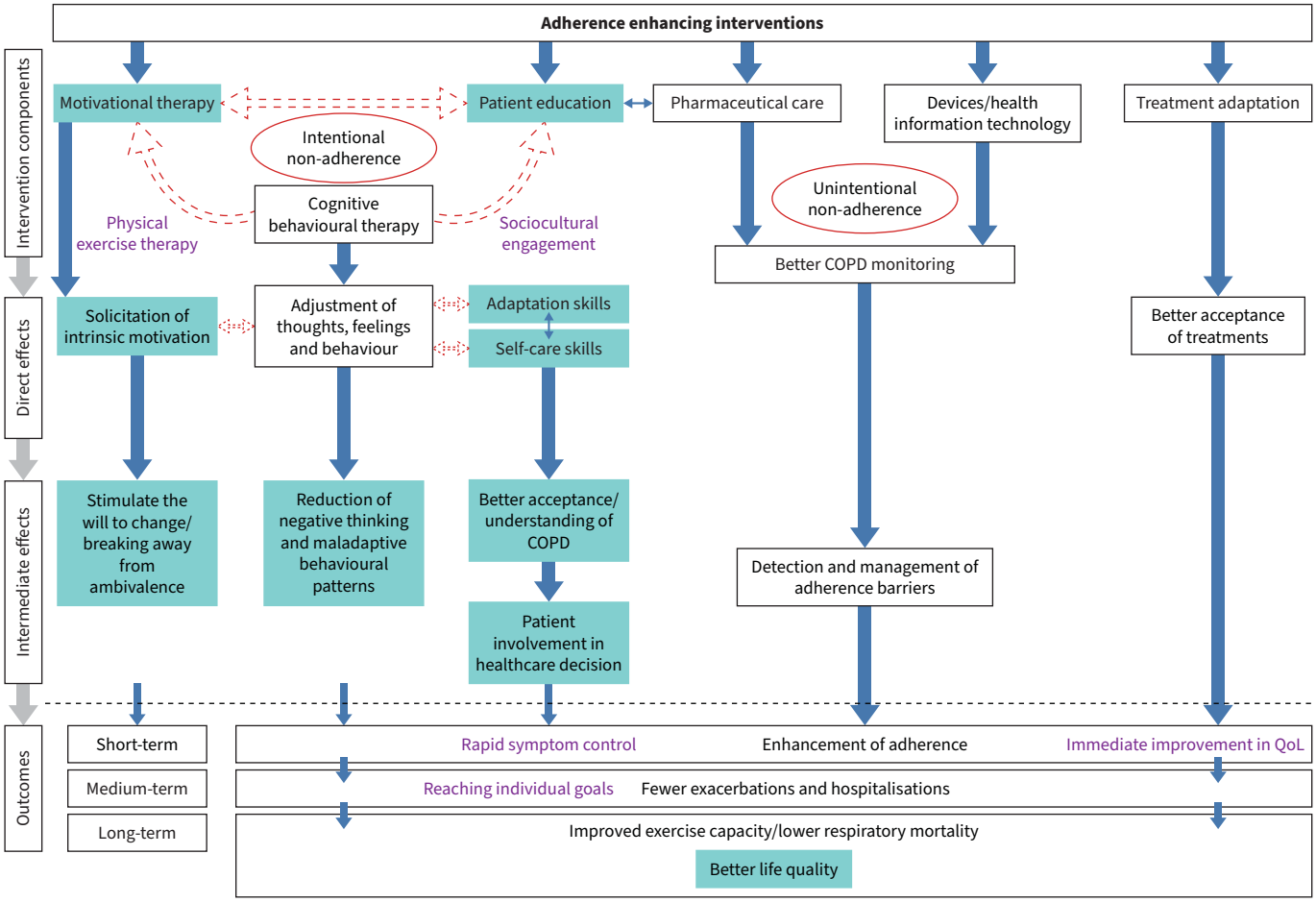

FIGURE 6 Process-oriented logic model supplemented by the patient concept on the topic of therapy adherence. Green squares represent areas of patient focus; purple text represents patient suggestions. QoL: quality of life.

Points for clinical practice

Education appears to be the most promising approach for increasing adherence to COPD treatment. Adding other components appears to have little benefit. The focus group interviews suggested self-efficacy, direct interactions and the importance of adequate training before telemedicine as important factors for therapy success.

Questions for future research

Further clinical trials should carry out head-to-head comparisons of different components of adherence interventions (single and multiple). In addition, it is critical that adherence measurements be standardised.

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Data sharing: We extracted the data of the included studies directly from the published reports. We did not request any data. We will share the data extraction forms on request. We will share our risk of bias assessment sheets in a file-sharing server on request. We have reported the PRISMA network meta-analysis checklist in appendix 11.

Author contributions: Co-ordination of the review: O. Ammous, T. Mathes. Search and collection of studies for inclusion in the review: O. Ammous, T. Mathes, R. Kampo, S. Salem. Conduct of patient interviews: M. Wollsching-Strobel, M. Zimmermann, D. Kroppen; Data extraction: O. Ammous, R. Kampo. Assessment of risk of

bias in the included studies: O. Ammous, R. Kampo. Data analysis: T. Mathes, R. Kampo. Assessment of the certainty of the evidence: O. Ammous, R. Kampo. Data interpretation: O. Ammous, S. Andreas, T. Friede, R. Kampo, S. Stanzel, M. Wollsching-Strobel, M. Zimmermann, S. Salem, W. Windisch, T. Mathes. Writing of the review: O. Ammous, T. Mathes, R. Kampo. Review of manuscript: O. Ammous, S. Andreas, T. Friede, R. Kampo, D. Kroppen, S. Stanzel, M. Wollsching-Strobel, M. Zimmermann, S. Salem, W. Windisch, T. Mathes. All authors read and approved the final manuscript.

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