ClinicalEvidence

COPD

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ABSTRACT

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Classically, it is thought to be a combination of emphysema and chronic bronchitis, although only one of these may be present in some people with COPD. The main risk factor for the development and deterioration of COPD is smoking. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of maintenance drug treatment in stable COPD? What are the effects of smoking cessation interventions in people with stable COPD? What are the effects of non-drug interventions in people with stable COPD? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 119 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: alpha$_1$ antitrypsin, antibiotics (prophylactic), anticholinergics (inhaled), beta$_2$ agonists (inhaled), corticosteroids (oral and inhaled), general physical activity enhancement, inspiratory muscle training, nutritional supplementation, mucolytics, oxygen treatment (long-term domiciliary treatment), peripheral muscle strength training, psychosocial and pharmacological interventions for smoking cessation, pulmonary rehabilitation, and theophylline.

QUESTIONS

INTERVENTIONS

DRUG TREATMENTS

Beneficial

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Unlikely to be beneficial

SMOKING CESSATION

Beneficial

Unknown effectiveness

NON-DRUG INTERVENTIONS

Beneficial

Likely to be beneficial

Unlikely to be beneficial

To be covered in future updates

Acute exacerbations of COPD

Vaccination against influenza and pneumococcus

Key points

- The main risk factor for the development and deterioration of chronic obstructive pulmonary disease (COPD) is smoking.
- Inhaled anticholinergics and beta$_2$ agonists improve lung function and symptoms and reduce exacerbations in stable COPD compared with placebo.

  It is unclear whether inhaled anticholinergics or inhaled beta$_2$ agonists are the more consistently effective drug class in the treatment of COPD.

  Short-acting anticholinergics seem to be associated with a small improvement in quality of life compared with beta$_2$ agonists.

  Long-acting inhaled anticholinergics may improve lung function compared with long-acting beta$_2$ agonists.

  Combined treatment with inhaled anticholinergics plus beta$_2$ agonists may improve symptoms and lung function and reduce exacerbations compared with either treatment alone, although long-term effects are unknown.
- Inhaled corticosteroids reduce exacerbations in COPD and reduce decline in FEV$_1$, but the beneficial effects are small.

  Oral corticosteroids may improve short-term lung function, but have serious adverse effects.

  Combined inhaled corticosteroids plus long-acting beta$_2$ agonists improve lung function, symptoms, and health-related quality of life, and reduce exacerbations compared with placebo, and may be more effective than either treatment alone.
- Long-term domiciliary oxygen treatment may improve survival in people with severe daytime hypoxaemia.
- Theophylline may improve lung function compared with placebo, but adverse effects limit its usefulness in stable COPD.
- We don't know whether mucolytic drugs, prophylactic antibiotics, or alpha$_1$ antitrypsin improve outcomes in people with COPD compared with placebo.
- Combined psychosocial and pharmacological interventions for smoking cessation can slow the deterioration of lung function, but have not been shown to reduce long-term mortality compared with usual care.
- Multi-modality pulmonary rehabilitation can improve exercise capacity, dyspnoea, and health-related quality of life in people with stable COPD; general physical exercises and peripheral muscle training can improve exercise capacity; inspiratory muscle training may improve lung function and exercise capacity; but nutritional supplementation has not been shown to be beneficial.

DEFINITION

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. [1] Classically, it is thought to be a combination of emphysema and chronic bronchitis, although only one of these may be present in some people with COPD. Emphysema is abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls, and without obvious fibrosis. Chronic bronchitis is chronic cough or mucous production for at least 3 months in at least 2 successive years when other causes of chronic cough have been excluded. [2]

INCIDENCE/ PREVALENCE

COPD mainly affects middle-aged and older people. In 1998, the WHO estimated that COPD was the fifth most common cause of death worldwide, responsible for 4.8% of all mortality (estimated 2,745,816 deaths in 2002), [3] and morbidity is increasing. Estimated prevalence in the USA rose by 41% between 1982 and 1994, and age-adjusted death rates rose by 71% between 1966 and 1985. All-cause age-adjusted mortality declined over the same period by 22% and mortality from cardiovascular diseases by 45%. [2] In the UK, physician-diagnosed prevalence was 2% in men and 1% in women between 1990 and 1997. [4]

AETIOLOGY/ RISK FACTORS

COPD is largely preventable. The main cause in developed countries is exposure to tobacco smoke. In developed countries, 85% to 90% of people with COPD have smoked at some point. [1] The disease is rare in lifelong non-smokers (estimated prevalence 5% in 3 large representative US surveys of non-smokers from 1971–1984), in whom "passive" exposure to environmental tobacco smoke has been proposed as a cause. [5] [6] Other proposed causes include bronchial hyper-responsiveness, indoor and outdoor air pollution, and allergy. [7] [8] [9]

PROGNOSIS

Airway obstruction is usually progressive in those who continue to smoke, resulting in early disability and shortened survival. Smoking cessation reverts the rate of decline in lung function to that of

non-smokers. [10] Many people will need medication for the rest of their lives, with increased doses and additional drugs during exacerbations.

AIMS OF INTERVENTION

To alleviate symptoms; to prevent exacerbations; to preserve optimal lung function; to improve activities of daily living, quality of life, and survival; with minimal adverse effects from treatment. [11]

OUTCOMES

Mortality; **lung function and exercise capacity**: short-term and long-term changes in lung function, including changes in FEV_1 ; peak expiratory flow; exercise tolerance; **COPD exacerbation and worsening of symptoms**: frequency, severity, and duration of exacerbations; symptom scores for dyspnoea; **quality of life**; and **adverse effects**. Scoring indices that evaluate both worsening of symptoms and quality-of-life scores include the St George's Respiratory Questionnaire, which is rated on a scale from 0 to 100 (a 4-point change is considered clinically important); the Transitional Dyspnoea Index, which is rated from –9 to +9 (a 1-point change is considered clinically important), and the Chronic Respiratory Disease Questionnaire (CRQ), which is rated from 1 to 7 (a 0.5-point change is considered clinically important). If systematic reviews or RCTs assessed individual components of these indices separately, we have reported these components under separate outcomes, for example the dyspnoea component of the CRQ under "COPD exacerbation and worsening of symptoms" and the emotive mastery component of the CRQ under "quality of life."

METHODS

Clinical Evidence search and appraisal April 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2010, Embase 1980 to April 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 2 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies, except for long-acting anticholinergics where a 6-month follow-up was required. We aimed for a minimum follow-up of 1 year for maintenance treatment, but, where we did not identify studies with this length of follow-up, reported on studies of shorter duration. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 95). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of maintenance drug treatment in stable COPD?

OPTION ANTICHOLINERGICS (INHALED)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Inhaled anticholinergics improve lung function and symptoms and reduce exacerbations in stable COPD compared with placebo.
- It is unclear whether inhaled anticholinergics or inhaled $beta_2$ agonists are the more consistently effective drug class in the treatment of COPD.
- Anticholinergics are associated with an increased rate of dry mouth.

Benefits and harms

Anticholinergics (short-term treatment) versus placebo:

We found 4 small [12] [13] [14] [15] and 4 large [16] [17] [18] [19] RCTs assessing the effects of ipratropium on lung function. Here, we report data from only the large RCTs. Two of the small RCTs [12] [13] found a significant effect in favour of ipratropium, and the remaining two [14] [15] found no significant difference among treatments. We also found one systematic review (search date 1999) assessing the effects on exercise capacity of any anticholinergic drug compared with placebo. [20] All the RCTs compared three or four interventions: ipratropium (at different doses in one trial), placebo, and a beta$_2$ agonist.

Lung function and exercise capacity

Anticholinergics (short-term treatment) compared with placebo Short-term treatment with ipratropium may be more effective at improving FEV$_1$ and exercise capacity (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[16] RCT **3-armed trial**	276 people The third arm assessed salmeterol	**Change in FEV$_1$, 12 weeks** with ipratropium (36 micrograms 4 times daily) with placebo Absolute results reported graphically	Reported as significant (ipratropium *v* placebo)	○○○	ipratropium
[17] RCT **3-armed trial**	405 people The third arm assessed salmeterol	**Change in FEV$_1$, 12 weeks** with ipratropium (36 micrograms 4 times daily) with placebo Absolute results reported graphically	Reported as significant (ipratropium *v* placebo)	○○○	ipratropium
[18] RCT **3-armed trial**	780 people The third arm assessed formoterol (eformoterol)	**Improvement in average FEV$_1$, over 12 hours after medication** with ipratropium (40 micrograms 4 times daily) with placebo Absolute results not reported	Difference between groups: 137 mL (ipratropium *v* placebo) 95% CI 88 mL to 186 mL	○○○	ipratropium
[18] RCT **3-armed trial**	780 people The third arm assessed formoterol (eformoterol)	**Morning pre-medication peak expiratory flow** with ipratropium (40 micrograms 4 times daily) with placebo Absolute results not reported	Difference between groups: –0.5 L/minute (ipratropium *v* placebo) 95% CI –7.4 L/minute to +6.5 L/minute P = 0.90	⟷	Not significant
Exercise capacity					
[20] Systematic review	Number of people not reported 17 RCTs in this analysis	**Changes in exercise capacity** with anticholinergic drugs with placebo Out of 17 RCTs, 16 found that any anticholinergic drug improved exercise capacity compared with placebo	Meta-analysis was not performed because of heterogeneity in design and outcomes assessed among studies		
[19] RCT **3-armed trial**	183 people with moderate to severe COPD, mean FEV$_1$ 40% predicted, mean age 64 years The third arm assessed formoterol	**Mean increase in shuttle walking distance , 12 weeks** 15.3 m with ipratropium (80 micrograms three times daily) 6.1 m with placebo Mean distance at baseline: 325 m	Reported as not significant (ipratropium *v* placebo) P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(18 micrograms twice daily)				

COPD exacerbation and worsening of symptoms

Anticholinergics (short-term treatment) compared with placebo Ipratropium in the short term seems no more effective at improving symptoms or the need for rescue bronchodilators (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for rescue bronchodilators					
[18] RCT **3-armed trial**	780 people The third arm assessed formoterol (eformoterol)	**Need for rescue medication** with ipratropium (40 micrograms 4 times daily) with placebo Absolute results not reported	P = 0.15 (ipratropium *v* placebo)	⟷	Not significant
Symptoms					
[18] RCT **3-armed trial**	780 people The third arm assessed formoterol (eformoterol)	**Symptoms** with ipratropium (40 micrograms 4 times daily) with placebo Absolute results not reported	P = 0.44 (ipratropium *v* placebo)	⟷	Not significant

No data from the following reference on this outcome. [16] [17] [19] [20]

Quality of life

Anticholinergics (short-term treatment) compared with placebo Short-term treatment with ipratropium is no more effective at improving quality of life (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life scores					
[18] RCT **3-armed trial**	780 people The third arm assessed formoterol (eformoterol)	**Quality-of-life scores** with ipratropium (40 micrograms 4 times daily) with placebo Absolute results not reported	Reported as not significant (ipratropium *v* placebo) P value not reported	⟷	Not significant

No data from the following reference on this outcome. [16] [17] [19] [20]

Mortality

No data from the following reference on this outcome. [16] [17] [18] [19] [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT	Number of people not reported	**Dry mouth** with ipratropium with placebo Absolute results not reported	P <0.05	○○○	placebo
[17] RCT **3-armed trial**	405 people The third arm assessed salmeterol	**Adverse effects affecting the ear, nose, and throat , 12 weeks** 58/138 (42%) with ipratropium (36 micrograms 4 times daily) 39/135 (29%) with placebo	P = 0.031 (ipratropium *v* placebo)	○○○	placebo
[18] RCT **3-armed trial**	780 people The third arm assessed formoterol (eformoterol)	**Adverse effects (any)** with ipratropium (40 micrograms 4 times daily) with placebo Absolute results not reported The RCT reported similar rates of adverse effects in the ipratropium and placebo groups The RCT reported that the most common adverse effects were viral infections, exacerbations of COPD, and headache			
[16] [19] RCT **3-armed trial**	459 people in total in the two RCTs The third arms assessed the effects of salmeterol [16] and formoterol [19]	**Adverse effects (any)** with ipratropium with placebo Absolute results not reported The two RCTs reported similar rates of adverse effects in the ipratropium and placebo groups	Significance not assessed in either RCT		

No data from the following reference on this outcome. [12] [13] [14] [20]

Anticholinergics (long-term treatment) versus placebo:

We found three systematic reviews (search dates 2009, [21] 2006, [22] and 2004 [23]) comparing tiotropium versus placebo, none of which specified a minimum follow-up of 6 months for inclusion of a study; and one additional RCT. [24]

Mortality

Anticholinergics (long-term treatment) compared with placebo Tiotropium seems no more effective at reducing all-cause mortality at 2 to 48 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[21] Systematic review	17,051 people with COPD 16 RCTs in this analysis	**All-cause mortality , 2 to 48 months** with tiotropium with placebo Absolute numbers not reported	RR 0.97 95% CI 0.86 to 1.09 P = 0.61	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[24] RCT	555 people aged at least 40 years with COPD	**All-cause mortality , 9 months** 3/266 (1%) with tiotropium 18 micrograms once daily 6/288 (2%) with placebo	Significance not assessed	○○○	

No data from the following reference on this outcome. [22] [23]

Lung function and exercise capacity

Anticholinergics (long-term treatment) compared with placebo Long-term treatment with tiotropium seems more effective at improving FEV_1 and FVC (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[22] Systematic review	4214 people with COPD 8 RCTs in this analysis	**Mean change in trough FEV_1 from baseline , 6 weeks to 12 months** with tiotropium with placebo Absolute numbers not reported	WMD 0.12 L 95% CI 0.11 L to 0.13 L P = 0.0001	○○○	tiotropium
[22] Systematic review	2375 people with COPD 7 RCTs in this analysis	**Mean change in trough FVC from baseline , 6 weeks to 12 months** with tiotropium with placebo Absolute numbers not reported	WMD 0.28 L 95% CI 0.25 L to 0.31 L P = 0.0001	○○○	tiotropium
[24] RCT	555 people aged at least 40 years with COPD	**Change in pre-dose FEV_1 , 9 months** with tiotropium 18 micrograms once daily with placebo Absolute results reported graphically	P = 0.0001	○○○	tiotropium
[24] RCT	555 people aged at least 40 years with COPD	**Change in pre-dose FVC , 9 months** with tiotropium 18 micrograms once daily with placebo Absolute results reported graphically	P <0.003	○○○	tiotropium
[24] RCT	555 people aged at least 40 years with COPD	**Change in pre-dose inspiratory capacity (IC) , 9 months** with tiotropium 18 micrograms once daily with placebo Absolute results reported graphically	P = 0.005	○○○	tiotropium

No data from the following reference on this outcome. [21] [23]

COPD exacerbation and worsening of symptoms

Anticholinergics (long-term treatment) compared with placebo Tiotropium used long term is more effective at 12 to 52 weeks at reducing COPD exacerbations (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbation					
[22] Systematic review	4280 people with COPD 8 RCTs in this analysis	**COPD exacerbations , 6 weeks to 12 months** 599/2249 (27%) with tiotropium 637/2031 (31%) with placebo	OR 0.76 95% CI 0.66 to 0.87 P = 0.0001	●○○	tiotropium
[24] RCT	555 people aged at least 40 years with COPD	**Mean annualised number of COPD exacerbations , 9 months** 1.05 with tiotropium 18 micro-grams once daily 1.83 with placebo	P = 0.03	○○○	tiotropium
[24] RCT	555 people aged at least 40 years with COPD	**Time to first exacerbation , during 9-month trial** 201 days with tiotropium 181 days with placebo	P <0.01	○○○	tiotropium

No data from the following reference on this outcome. [21] [23]

Quality of life

Anticholinergics (long-term treatment) compared with placebo Long-term treatment with tiotropium seems more effective at 6 to 12 months at improving quality of life (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[22] Systematic review	1831 people with COPD 3 RCTs in this analysis	**Mean change in St George's Respiratory Questionnaire (SGRQ) , 6 to 12 months** with tiotropium with placebo Absolute numbers not reported	WMD –3.35 95% CI –4.54 to –2.16 P = 0.0001	○○○	tiotropium
[24] RCT	555 outpatients aged at least 40 years with COPD	**Mean change in SGRQ , 9 months** –8.5 units with tiotropium 18 mi-crograms once daily –4.3 units with placebo See further information on studies for details regarding this outcome	P <0.05	○○○	tiotropium

No data from the following reference on this outcome. [21] [23]

Adverse effects

No data from the following reference on this outcome. [21] [22] [23] [24]

Ipratropium plus smoking cessation programme versus smoking cessation programme plus usual care:
See option on psychosocial plus drug interventions in effects of advice to stop smoking, p 66 . For adverse effects of ipratropium, see harms of short-term treatment with ipratropium above.

Inhaled anticholinergics versus beta$_2$ agonists:
See option on inhaled anticholinergics versus beta$_2$ agonists, p 24 .

Inhaled anticholinergic alone versus inhaled anticholinergics plus beta$_2$ agonists:
See option on inhaled anticholinergics plus beta$_2$ agonists, p 18 .

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] Systematic review	2052 people with COPD 4 RCTs in this analysis	**Dry mouth , 6 weeks to 12 months** 12% with tiotropium 3% with placebo Absolute numbers not reported	OR 4.56 95% CI 2.95 to 7.06 P = 0.0001	●●○	placebo
[23] Systematic review	1675 person-years; 7819 people in the systematic review; number of RCTs and people in this analysis not specified	**Arrhythmia other than tachycardia or atrial fibrillation , 3 months to >6 months** 1.31 per 100 person-years with tiotropium 0.49 per 100 person-years with placebo Absolute numbers not reported	RR 2.71 95% CI 1.1 to 6.65 P <0.05	●●○	placebo
[23] Systematic review	1675 person-years; 7819 people in the systematic review; number of RCTs and people in this analysis not specified	**Urinary retention , 3 months to >6 months** 0.78 per 100 person-years with tiotropium 0.08 per 100 person-years with placebo Absolute numbers not reported	RR 10.93 95% CI 1.26 to 94.9 P <0.05	●●●	placebo
[24] RCT	555 people aged at least 40 years with COPD	**Proportion of people with at least one adverse effect , 9 months** 162/266 (61%) with tiotropium 18 micrograms once daily 193/288 (67%) with placebo	Significance not assessed		

No data from the following reference on this outcome. [21]

Further information on studies

[24] The primary quality-of-life outcome assessed by the RCT was the proportion of people achieving the minimum important difference of 4 units in SGRQ. We report mean change in score to allow better comparison with the other RCT we report.

Comment: The systematic reviews included some RCTs with a follow-up of less than the 6 months specified in the *Clinical Evidence* inclusion criteria for the comparison of tiotropium compared with placebo. One review included 4392 patients followed for 6 months or longer, 108 followed for 25 weeks, and 1578 followed for <6 months; [22] however, we have reported it because the follow-up period was sufficient in most participants. For one review, we have reported analysis of adverse effects only. [23] This review included several shorter trials, with only 52% of patients exposed to tiotropium for >6 months. [23] Data from the other review [21] demonstrated through sensitivity analysis that duration of follow-up (whether >6 months or <6 months) did not affect the conclusions regarding cardiovascular adverse events or overall mortality. [21] We have not reported one well-publicised review of the cardiovascular safety of anticholinergics because it pooled ipratropium with tiotropium, and placebo with active-treatment comparisons. [25]

OPTION BETA2 AGONISTS (INHALED)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Inhaled $beta_2$ agonists improve lung function and symptoms and reduce exacerbations in stable COPD compared with placebo.
- It is unclear whether inhaled anticholinergics or inhaled $beta_2$ agonists are the more consistently effective drug class in the treatment of COPD.

Benefits and harms

Short-acting $beta_2$ agonists (short-term treatment) versus placebo:

We found two systematic reviews (search dates 2002 [26] and 2004 [27]) and one subsequent RCT. [28]

Lung function and exercise capacity

Compared with placebo Short-acting $beta_2$ agonists (short-term treatment) may be more effective at increasing FEV_1 in people with stable COPD, but we don't know whether they are more effective at increasing exercise tolerance (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[26] Systematic review	196 people 6 RCTs in this analysis	**FEV_1** with short-acting $beta_2$ agonists (delivered by metered-dose inhaler) with placebo Absolute results not reported	WMD 0.14 L 95% CI 0.04 L to 0.25 L The trials were small and the results heterogeneous The meta-analysis used post-crossover results, but because the treatment is short acting there is unlikely to be persistence of treatment effects after crossover	○○○	short-acting $beta_2$ agonists
[28] RCT **4-armed trial**	209 people with COPD The remaining arms assessed levosalbutamol (levalbuterol) 1.25 mg and racemic salbutamol (albuterol) 2.5 mg	**% change in area under the curve (AUC) in FEV_1 , 6 weeks** 10.5% with levosalbutamol 0.63 mg three times daily 1.6% with placebo 108 people in this assessment	P <0.003	○○○	levosalbutamol 0.63 mg
[28]	209 people with COPD	**% change in AUC in FEV_1 , 6 weeks**	P <0.003	○○○	levosalbutamol 1.25 mg

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
RCT **4-armed trial**	The remaining arms assessed levosalbutamol 0.63 mg and racemic salbutamol 2.5 mg	9.2% with levosalbutamol 1.25 mg three times daily 1.6% with placebo 104 people in this analysis			
[28] RCT **4-armed trial**	209 people with COPD The remaining arms assessed levosalbutamol 0.63 mg and 1.25 mg	**% change in AUC in FEV_1 , 6 weeks** 15.3% with racemic salbutamol 2.5 mg three times daily 1.6% with placebo 107 people in this analysis	P <0.003	○○○	racemic salbutamol 2.5 mg
Exercise capacity					
[26] Systematic review	188 people 4 RCTs in this analysis	**Distance walked** with short-acting $beta_2$ agonists (delivered by metered-dose inhaler) with placebo Absolute results not reported	SMD +0.18 m 95% CI –0.11 m to +0.47 m The trials were small and the results heterogeneous The meta-analysis used post-crossover results, but, because the treatment is short acting, there is unlikely to be persistence of treatment effects after crossover	⟷	Not significant

No data from the following reference on this outcome. [27]

COPD exacerbation and worsening of symptoms

Compared with placebo Short-acting $beta_2$ agonists (short-term treatment) may be more effective at improving daily breathlessness scores in people with stable COPD (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[26] Systematic review	188 people 4 RCTs in this analysis	**Daily breathlessness score** with short-acting $beta_2$ agonists (delivered by metered-dose inhaler) with placebo Absolute results not reported	WMD –1.33 95% CI –1.65 to –1.01 P <0.001 The trials were small and the results heterogeneous The meta-analysis used post-crossover results, but, because the treatment is short acting, there is unlikely to be persistence of treatment effects after crossover	○○○	short-acting $beta_2$ agonists
[28] RCT **4-armed trial**	209 people with COPD	**Withdrawals because of COPD exacerbations** 2% with levosalbutamol 0.63 mg three times daily 4% with levosalbutamol 1.25 mg three times daily 10% with racemic salbutamol 2.5 mg three times daily 0% with placebo Absolute numbers not reported	P = 0.01 for racemic salbutamol *v* placebo Significance not assessed for either dose of levosalbutamol *v* placebo	○○○	placebo

No data from the following reference on this outcome. [27]

Mortality

No data from the following reference on this outcome. [26] [27] [28]

Quality of life

No data from the following reference on this outcome. [26] [27] [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[27] Systematic review	15,276 people with asthma or COPD 22 RCTs in this analysis	**Adverse cardiovascular events** with beta$_2$ agonists (short- and long-acting) with placebo Absolute results not reported	RR 2.54 95% CI 1.59 to 4.05	●●○	placebo
[27] Systematic review	386 people with asthma or COPD 11 RCTs in this analysis	**Increased heart rate** with beta$_2$ agonists (single dose of either short- or long-acting) with placebo Absolute results not reported	WMD 9.12 95% CI 5.32 to 12.92	○○○	placebo
[27] Systematic review	168 people with asthma or COPD 6 RCTs in this analysis	**Reduction in serum potassium concentration** with beta$_2$ agonists (single dose of either short- or long-acting) with placebo Absolute results not reported	WMD –0.36 95% CI –0.54 to –0.18	○○○	placebo

No data from the following reference on this outcome. [26] [28]

Short-acting beta$_2$ agonists (long-term treatment) versus placebo:

We found no systematic review of only long-term treatment with short-acting beta$_2$ agonists versus placebo.

Long-acting beta$_2$ agonists (short-term or long-term treatment) versus placebo:

We found no review on only short-term (follow-up <6 months) or only long-term (>6 months) treatment with long-acting beta$_2$ agonists compared with placebo. We found 4 systematic reviews (search dates 2002, [29] 2005, [30] [31] and 2007 [32]), 5 additional RCTS, [19] [33] [34] [35] [36] and 5 subsequent RCTs that combined data on a range of treatment duration. [37] [38] [39] [40] [41] In addition, we found one systematic review that reported on adverse effects. [27]

Mortality

Compared with placebo Long-acting beta$_2$ agonists (short-term or long-term treatment) seem no more effective at reducing mortality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[32] Systematic review	8400 people with COPD 13 RCTs in this analysis	**All-cause mortality , 1 to 36 months** 4.9% with long-acting beta$_2$ agonist 6.5% with placebo Absolute numbers not reported	RR 1.6 95% CI 0.8 to 2.4 P >0.05	⟷	Not significant

No data from the following reference on this outcome. [29] [30] [31] [19] [33] [34] [35] [36] [37] [38] [39] [40] [41]

Lung function and exercise capacity

Compared with placebo Long-acting beta$_2$ agonists (short-term or long-term treatment) seem more effective at improving lung function, but we don't know whether they are more effective at improving capacity for exercise (endurance time and shuttle walking distance) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[34] RCT	657 people with COPD	**Change in FEV$_1$ from baseline , 6 months** +5% with formoterol 9 micrograms twice daily –1.4% with placebo Both groups were allowed to take terbutaline 0.5 mg as needed	AR 6.5% 95% CI 2.5% to 10.7% P <0.01	○○○	formoterol
[37] RCT **5-armed trial**	717 people with COPD	**Change in pre-dose FEV$_1$ from baseline , 12 weeks** +16.9% with arformoterol 15 micrograms twice daily +18.9% with arformoterol 25 micrograms twice daily +14.9% with arformoterol 50 micrograms once daily +17.4% with salmeterol 42 micrograms twice daily +6.0% with placebo	P <0.001 for all active treatments *v* placebo	○○○	long-acting beta$_2$ agonist
[38] RCT **3-armed trial**	163 people with COPD	**Change in pre-dose FEV$_1$ from baseline , 28 days** +220 mL with indacaterol 400 micrograms once daily +210 mL with indacaterol 800 micrograms once daily Placebo value for change in FEV$_1$ not reported	P <0.0001 for either dose of indacaterol *v* placebo	○○○	indacaterol
Exercise capacity					
[19] RCT **3-armed trial**	183 people with moderate to severe COPD In review [29] [30]	**Increase shuttle walking test (increase in distance from baseline) , 12 weeks** 20.4 m with formoterol 18 micrograms twice daily	Reported as not significant (formoterol *v* placebo) P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The third arm assessed ipratropium	6.0 m with placebo Baseline mean distance was 325 m			
[39] RCT **Crossover design**	20 people with clinically stable COPD	**Mean difference in endurance shuttle walking test (ESWT) , 2.5 hours post treatment** with salmeterol 50 micrograms single dose with placebo single dose Absolute numbers not reported Mean distance walked was 160 m more with salmeterol than with placebo People received standardised instructions to walk for as long as possible, with a predetermined 20-minute maximum	P = 0.02	○○○	salmeterol
[36] RCT **Crossover design**	23 people with moderate to severe COPD (mean FEV_1 42% predicted) In review [29] [30]	**Difference in peak exercise endurance time , 12 weeks** with salmeterol 50 micrograms (inhaled) with placebo Absolute results not reported	Difference between groups of 96 seconds P = 0.02	○○○	salmeterol
[33] RCT **Crossover design** **5-armed trial**	34 people The fifth arm assessed ipratropium (80 micrograms three times daily)	**Time to exhaustion , 1 week** 10.94 minutes with formoterol 4.5 micrograms 10.78 minutes with formoterol 9 micrograms 10.59 minutes with formoterol 18 micrograms 10.20 minutes with placebo	P <0.0001 (formoterol 4.5 micrograms *v* placebo) P <0.01 (formoterol 9 micrograms *v* placebo) P <0.05 (formoterol 18 micrograms *v* placebo)	○○○	formoterol

No data from the following reference on this outcome. [31] [32] [35] [40] [41]

COPD exacerbation and worsening of symptoms

Compared with placebo Long-acting $beta_2$ agonists (short-term or long-term treatment) seem more effective at reducing the rate of COPD exacerbations and at improving symptoms (assessed by the Chronic Disease Respiratory Questionnaire and Transitional Dyspnoea Index) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[32] Systematic review	6453 people with COPD 14 RCTs in this analysis	**Cumulative incidence of severe COPD exacerbations , 1 to 36 months** 7.5% with long-acting $beta_2$ agonist 10.8% with placebo Absolute numbers not reported	RR 0.80 (random effects model) 95% CI 0.69 to 0.82	●○○	long-acting $beta_2$ agonist
[37] RCT **5-armed trial**	717 people with COPD	**Frequency of COPD exacerbations** 19/141 (13.5%) with arformoterol 15 micrograms twice daily	P >0.05 for all treatments *v* placebo	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		19/143 (13.3%) with arformoterol 25 micrograms twice daily 17/146 (11.6%) with arformoterol 50 micrograms once daily 20/144 (13.9%) with salmeterol 42 micrograms twice daily 24/143 (16.8%) with placebo Double-dummy trial			
[38] RCT **3-armed trial**	163 people with COPD	**Number of COPD exacerbations , 28 days** 3/68 (4%) with indacaterol 400 micrograms 0/67 (0%) with indacaterol 800 micrograms 2/28 (7%) with placebo	Significance not assessed		
Symptom severity					
[30] Systematic review	545 people 2 RCTs in this analysis	**Improvement in the Chronic Respiratory Disease Questionnaire (CRQ)** with long-acting beta$_2$ agonists with placebo Absolute results not reported Long-acting beta$_2$ agonists assessed by the review were salmeterol and formoterol	OR 1.71 95% CI 1.21 to 2.42 P = 0.002	●○○	long-acting beta$_2$ agonists
[30] Systematic review	736 people 2 RCTs in this analysis	**Improvement in transitional dyspnoea index (TDI)** with long-acting beta$_2$ agonists with placebo Absolute results not reported Long-acting beta$_2$ agonists assessed by the review were salmeterol and formoterol	OR 1.70 95% CI 1.25 to 2.31 P = 0.0008	●○○	long-acting beta$_2$ agonists

No data from the following reference on this outcome. [29] [31] [19] [33] [34] [35] [36] [39] [40] [41]

Quality of life

Compared with placebo Long-acting beta$_2$ agonists (short-term or long-term treatment) may be no more effective at improving quality of life (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[32] Systematic review	6453 people with COPD 14 RCTs in this analysis	**Mean change in St George's Respiratory Questionnaire , 1 to 36 months** with long-acting beta$_2$ agonist (salmeterol or formoterol) with placebo Absolute numbers not reported	WMD –3.26 95% CI –4.57 to –1.96	○○○	long-acting beta$_2$ agonist

No data from the following reference on this outcome. [29] [30] [31] [19] [33] [34] [35] [36] [37] [38] [39] [40] [41]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] Systematic review	2404 people with COPD 4 RCTs in this analysis	**Mortality attributed to treatment-related respiratory problems** 21/1320 (2%) with long-acting beta$_2$ agonist 8/1084 (1%) with placebo	RR 2.47 95% CI 1.12 to 5.45 P = 0.03	●●○	placebo
[30] Systematic review	5055 people 12 RCTs in this analysis	**Proportion of people who withdrew because of an adverse effect** with long-acting beta$_2$ agonists with placebo Absolute results not reported The most common immediate adverse effect is tremor, which is usually worse in the first few days of treatment	OR 0.86 95% CI 0.72 to 1.02 P = 0.09	⟷	Not significant
[34] RCT	657 people with COPD	**Rate of adverse effects (rates/1000 treatment days) , 6 months** 3.8 with formoterol 9 micrograms twice daily 4.5 with placebo Both groups were allowed to take terbutaline 0.5 mg as needed No further information on adverse effects was given	Significance not assessed		
[35] RCT **4-armed trial**	6184 people with COPD; 6112 people included in efficacy analysis The third arm assessed salmeterol 50 micrograms once daily plus fluticasone 500 micrograms twice daily and the fourth arm assessed fluticasone alone (500 micrograms twice daily) alone	**Proportion of people experiencing a drug-related adverse effect** 12% with salmeterol (50 micrograms twice daily) 13% with placebo Absolute numbers not reported 3045 people in this analysis; includes people who had discontinued study medication The most common adverse effect reported was COPD exacerbation	Significance not assessed		
[27] Systematic review	15,276 people with asthma or COPD 22 RCTs in this analysis	**Adverse cardiovascular events** with beta$_2$ agonists (short- and long-acting) with placebo Absolute results not reported	RR 2.54 95% CI 1.59 to 4.05	●●○	placebo
[27] Systematic review	386 people with asthma or COPD 11 RCTs in this analysis	**Increased heart rate** with beta$_2$ agonists (single dose of either short- or long-acting) with placebo Absolute results not reported	WMD 9.12 95% CI 5.32 to 12.92	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[40] RCT **5-armed trial**	1465 people with COPD	**Heart rate difference from baseline , 12 weeks** –2.4 bpm with arformoterol 15 micrograms twice daily –0.6 bpm with arformoterol 25 micrograms twice daily –0.3 bpm with arformoterol 50 micrograms once daily –0.0 bpm with salmeterol 42 micrograms twice daily –1.8 bpm with placebo Pooled results of 2 identically designed phase III RCTs Rates of atrial tachycardia, atrial fibrillation or flutter, and non-sustained and sustained ventricular tachycardia did not increase with long-acting beta$_2$ agonist compared with placebo	P >0.05 for any active treatment *v* placebo	⟷	Not significant
[41] RCT **3-armed trial**	351 people with COPD	**Arrhythmia , 12 weeks** with formoterol 20 micrograms nebulised twice daily with formoterol 12 micrograms dry powder twice daily with placebo Absolute numbers not reported Baseline heart rate and rates of atrial tachycardia, atrial fibrillation, and ventricular tachycardia did not increase with formoterol compared with placebo	P >0.05 for either dose of formoterol *v* placebo	⟷	Not significant
[27] Systematic review	168 people with asthma or COPD 6 RCTs in this analysis	**Reduction in serum potassium concentration** with beta$_2$ agonists (single dose of either short- or long-acting) with placebo Absolute results not reported	WMD –0.36 95% CI –0.54 to –0.18	○○○	placebo

No data from the following reference on this outcome. [29] [32] [33] [36] [37] [38] [19] [39]

Beta$_2$ agonists versus inhaled anticholinergics:

See option on inhaled anticholinergics versus beta$_2$ agonists, p 24 .

Beta$_2$ agonists alone versus inhaled anticholinergics plus beta$_2$ agonists:

See option on inhaled anticholinergics plus beta$_2$ agonists, p 18 .

Beta$_2$ agonists alone versus inhaled corticosteroids plus beta$_2$ agonists:

See option on inhaled corticosteroids plus beta$_2$ agonists, p 41 .

Further information on studies

[30] Owing to heterogeneity among studies in reporting of effects on FEV_1, the review did not pool data for this outcome. However, the review reported that most RCTs found an improvement in FEV_1 with long-acting $beta_2$ agonists compared with placebo. The review reported that RCTs found no significant difference between long-acting $beta_2$ agonists and placebo in effects on exercise as measured by various walking tests, but the review did not pool data for this comparison.

[35] The RCT also carried out a last observation carried forward analysis for the outcome of FEV_1. However, the withdrawal rate from the RCT was high and the proportion of people followed up at 3 years for this outcome was 56% (851/1524) in the placebo group, and 63% (960/1521) in the salmeterol alone group. These follow-up rates are below *Clinical Evidence* reporting criteria of 80%, and so these data are not reported here.

Comment: **Clinical guide:**
High doses of $beta_2$ agonists can reduce plasma potassium, cause dysrhythmia, and reduce arterial oxygen tension. [42] The risk of adverse events may be higher in people with pre-existing cardiac arrhythmias and hypoxaemia. [43]

OPTION ANTICHOLINERGICS PLUS BETA2 AGONISTS (INHALED)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Combined treatment with inhaled anticholinergics and $beta_2$ agonists may improve symptoms and lung function and reduce exacerbations compared with either treatment alone, although long-term effects are unknown.
- We found no clinically important information from RCTs comparing long-term treatment with a combination of anticholinergics and $beta_2$ agonists versus no active treatment.

Benefits and harms

Short-acting anticholinergic plus short-acting inhaled $beta_2$ agonist (short-term treatment) versus short-acting $beta_2$ agonist alone:

We found two systematic reviews (search date 2002, 3 RCTs, 1399 people; [29] and search date 2008, 7 RCTs, 2252 people). [44] The second review assessed the effects of ipratropium plus short-acting inhaled $beta_2$ agonist (metaproterenol, fenoterol, and salbutamol), and identified the three RCTs identified by the first review, but reported on different outcomes. [44]

Lung function and exercise capacity

Short-acting anticholinergic plus short-acting inhaled $beta_2$ agonist (short-term treatment) compared with short-acting $beta_2$ agonist alone Ipratropium plus a short-acting $beta_2$ agonist seems more effective than short-acting $beta_2$ agonist alone at improving FEV_1 after 85 days of treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[44] Systematic review	2248 people 7 RCTs in this analysis	**Mean peak FEV_1 response , 85 days** with ipratropium plus short-acting $beta_2$ agonist with short-acting $beta_2$ agonist alone Absolute results not reported	WMD 0.07 L 95% CI 0.05 L to 0.09 L P <0.0001	○○○	ipratropium plus short-acting $beta_2$ agonist

No data from the following reference on this outcome. [29]

COPD exacerbation and worsening of symptoms

Short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist (short-term treatment) compared with a short-acting beta$_2$ agonist alone Combining a short-acting anticholinergic drug (ipratropium) with a short-acting beta$_2$ agonist for 12 weeks is more effective at improving exacerbations, but ipratropium plus a short-acting beta$_2$ agonist seems no more effective at 85 days at improving the dyspnoea component of the Chronic Respiratory Disease Questionnaire (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[29] Systematic review	1399 people 3 RCTs in this analysis	**COPD exacerbations , 12 weeks** with short-acting anticholinergic (ipratropium) plus short-acting beta$_2$ agonist with short-acting beta$_2$ agonist alone Absolute results not reported	RR 0.68 95% CI 0.51 to 0.91	●○○	short-acting anti-cholinergic plus short-acting beta$_2$ agonist
Symptom severity					
[44] Systematic review	1529 people 5 RCTs in this analysis	**Dyspnoea component of the Chronic Respiratory Disease Questionnaire (CRQ) , 85 days** with ipratropium plus short-acting beta$_2$ agonist with short-acting beta$_2$ agonist alone Absolute results not reported	WMD +0.01 95% CI –0.06 to +0.08 P = 0.8	⟷	Not significant

Quality of life

Short-acting anticholinergic plus a short-acting inhaled beta$_2$ agonist (short-term treatment) compared with a short-acting beta$_2$ agonist alone Ipratropium plus a short-acting beta$_2$ agonist seems no more effective than short-acting beta$_2$ agonist alone at 85 days at improving fatigue, emotion, and mastery components of the Chronic Respiratory Disease Questionnaire (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[44] Systematic review	1529 people 5 RCTs in this analysis	**Fatigue component of the Chronic Respiratory Disease Questionnaire (CRQ) , 85 days** with ipratropium plus short-acting beta$_2$ agonist with short-acting beta$_2$ agonist alone Absolute results not reported	WMD +0.01 95% CI –0.10 to +0.13 P = 0.8	⟷	Not significant
[44] Systematic review	1529 people 5 RCTs in this analysis	**Emotion component of the CRQ , 85 days** with ipratropium plus short-acting beta$_2$ agonist with short-acting beta$_2$ agonist alone Absolute results not reported	WMD +0.02 95% CI –0.12 to +0.16 P = 0.8	⟷	Not significant
[44] Systematic review	1529 people 5 RCTs in this analysis	**Mastery component of the CRQ , 85 days** with ipratropium plus short-acting beta$_2$ agonist with short-acting beta$_2$ agonist alone	WMD +0.03 95% CI –0.09 to +0.15 P = 0.6	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			

No data from the following reference on this outcome. [29]

Mortality

No data from the following reference on this outcome. [29] [44]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[44] Systematic review	1588 people 5 RCTs in this analysis	**Proportion of people reporting an adverse effect** 112/789 (14%) with ipratropium plus short-acting beta$_2$ agonist 96/769 (13%) with short-acting inhaled beta$_2$ agonist	RR 1.13 95% CI 0.88 to 1.45 P = 0.3	⟷	Not significant

No data from the following reference on this outcome. [29]

Short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist (short-term treatment) versus short-acting anticholinergic alone:

We found one systematic review (search date 2002, 3 RCTs, 1399 people). [29]

COPD exacerbation and worsening of symptoms

Short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist (short-term treatment) compared with a short-acting anticholinergic alone Combining a short-acting anticholinergic drug (ipratropium) with a short-acting beta$_2$ agonist for 12 weeks seems as effective a short-acting anticholinergic alone at improving exacerbations (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[29] Systematic review	1186 people 2 RCTs in this analysis	**COPD exacerbations , 12 weeks** with short-acting anticholinergic plus beta$_2$ agonist with short-acting anticholinergic alone Absolute results not reported	RR 1.04 95% CI 0.65 to 1.68	⟷	Not significant

Mortality

No data from the following reference on this outcome. [29]

Lung function and exercise capacity

No data from the following reference on this outcome. [29]

Quality of life

No data from the following reference on this outcome. [29]

Adverse effects

No data from the following reference on this outcome. [29]

Short-acting anticholinergic plus long-acting inhaled beta$_2$ agonist (short-term treatment) versus beta$_2$ agonist alone:

We found one systematic review (search date 2008, 3 RCTs, 1610 people). [45] The review, which included unpublished data from drug companies, did not pool data for many outcomes. Two of the RCTs identified by the review were unpublished and so are not reported further.

Lung function and exercise capacity

Short-acting anticholinergic plus long-acting inhaled beta$_2$ agonist (short-term treatment) compared with beta$_2$ agonist alone Combining a short-acting anticholinergic with a long-acting beta$_2$ agonist may be modestly more effective that beta$_2$ agonist alone at improving FEV$_1$ (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function (FEV$_1$)					
[46] RCT	94 people In review [45]	**Mean improvement in FEV$_1$ as a percentage of predicted FEV$_1$, 12 weeks** 8% with salmeterol (50 micrograms twice daily) plus ipratropium (40 micrograms 4 times daily) 5% with salmeterol alone (50 micrograms twice daily)	P <0.01	○○○	salmeterol plus ipratropium

Mortality

No data from the following reference on this outcome. [45] [46]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [45] [46]

Quality of life

No data from the following reference on this outcome. [45] [46]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] Systematic review	936 people 3 RCTs in this analysis	**Proportion of people reporting a treatment-related adverse effect** 205/473 (43%) with salmeterol plus ipratropium 192/483 (40%) with salmeterol alone	RR 1.04 95% CI 0.90 to 1.21 P = 0.6	⟷	Not significant

Short-acting anticholinergic plus long-acting inhaled beta$_2$ agonist (short-term treatment) versus short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist:

We found one cross-over RCT. [47]

Lung function and exercise capacity

Short-acting anticholinergic plus a long-acting inhaled beta$_2$ agonist (short-term treatment) compared with a short-acting anticholinergic plus a short-acting inhaled beta$_2$ agonist Formoterol plus ipratropium may be more effective than salbutamol plus ipratropium at 3 weeks at improving FEV$_1$ and peak expiratory flow rates (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[47] RCT **Crossover design**	172 people	**Improvement in pre-medication FEV$_1$ from baseline , 3 weeks** with ipratropium (40 micrograms 4 times daily) plus formoterol (12 micrograms twice daily) with ipratropium (40 micrograms 4 times daily) plus salbutamol (200 micrograms 4 times daily) Absolute results not reported	116 mL 95% CI 83 mL to 150 mL	○○○	ipratropium plus formoterol
[47] RCT **Crossover design**	172 people	**Improvement in mean morning peak expiratory flow from baseline over the previous 7 days , 3 weeks** with ipratropium (40 micrograms 4 times daily) plus formoterol (12 micrograms twice daily) with ipratropium (40 micrograms 4 times daily) plus salbutamol (200 micrograms 4 times daily) Absolute results not reported	12 L/minute 95% CI 6 L/minute to 19 L/minute	○○○	ipratropium plus formoterol

Mortality

No data from the following reference on this outcome. [47]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] RCT **Crossover design**	172 people	**Proportion of people reporting adverse effects** 16/172 (10%) with ipratropium (40 micrograms 4 times daily) plus formoterol (12 micrograms twice daily) 22/172 (13%) with ipratropium (40 micrograms 4 times daily) plus salbutamol (200 micrograms 4 times daily)	Significance not assessed		
[47] RCT **Crossover design**	172 people	**Proportion of people reporting dyspnoea** 2/172 (1%) with ipratropium (40 micrograms 4 times daily) plus formoterol (12 micrograms twice daily) 5/172 (3%) with ipratropium (40 micrograms 4 times daily) plus salbutamol (200 micrograms 4 times daily) Dyspnoea was one of most common adverse effects reported	Significance not assessed		
[47] RCT **Crossover design**	172 people	**Proportion of people reporting exacerbation of obstructive airway disease** 0/172 (0%) with ipratropium (40 micrograms 4 times daily) plus formoterol (12 micrograms twice daily) 5/172 (3%) with ipratropium (40 micrograms 4 times daily) plus salbutamol (200 micrograms 4 times daily) Exacerbation was one of most common adverse effects reported	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[47] RCT **Crossover design**	172 people	**Proportion of people reporting pharyngitis** 1/172 (1%) with ipratropium (40 micrograms 4 times daily) plus formoterol (12 micrograms twice daily) 3/172 (2%) with ipratropium (40 micrograms 4 times daily) plus salbutamol (200 micrograms 4 times daily) Pharyngitis was one of most common adverse effects reported	Significance not assessed		

Anticholinergic plus inhaled beta$_2$ agonists (long-term treatment):

We found no review or RCTs of long-term treatment with anticholinergics plus beta$_2$ agonists compared with placebo or either drug alone.

Further information on studies

[46] Adverse effects data from the RCT are included in the meta-analysis of adverse effects carried out by the review and so are not discussed separately.

Comment: None.

OPTION ANTICHOLINERGICS VERSUS BETA2 AGONISTS (INHALED)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- It is unclear whether inhaled anticholinergics or inhaled beta$_2$ agonists are the more consistently effective drug class in the treatment of COPD.
- Short-acting anticholinergics seem to be associated with a small improvement in quality of life compared with beta$_2$ agonists.
- Long-acting inhaled anticholinergic drugs may improve lung function compared with long-acting beta$_2$ agonists.
- We found no clinically important results from RCTs comparing long-acting anticholinergics versus short-acting beta$_2$ agonists in the treatment of people with COPD.

Benefits and harms

Short-acting anticholinergic versus short-acting beta$_2$ agonist:

We found 5 systematic reviews comparing anticholinergics versus beta$_2$ agonists. [29] [48] [30] [44] [45] The reviews did not report data in terms of short- or long-term duration of treatment as defined in our Methods section, but by length of drug action. We report comparisons as reported in the reviews, and specify the duration of treatment where possible. One review compared anticholinergics as a class versus beta$_2$ agonists as a class (see further information on studies for results). [30] One review (search date 2008, 11 RCTs, 3912 people) compared ipratropium versus short-acting beta$_2$ agonists (metaproterenol, fenoterol, and salbutamol). [44]

Lung function and exercise capacity

Short-acting anticholinergic compared with short-acting beta$_2$ agonist Ipratropium and short-acting beta$_2$ agonists seem equally effective at 85 days at improving FEV$_1$ (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[44] Systematic review	1917 people 6 RCTs in this analysis	**Mean FEV_1 peak response , 85 days of treatment** with ipratropium with short-acting beta$_2$ agonists Absolute results not reported	WMD 0.00 L 95% CI –0.02 L to +0.01 L P = 0.6	⟷	Not significant

COPD exacerbation and worsening of symptoms

Short-acting anticholinergic compared with short-acting beta$_2$ agonist Ipratropium seems modestly more effective than a short-acting beta$_2$ agonist at improving the dyspnoea component of the Chronic Respiratory Disease Questionnaire (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[44] Systematic review	1529 people 5 RCTs in this analysis	**Improvement in the dyspnoea component of the Chronic Respiratory Disease Questionnaire , 85 days of treatment** with ipratropium with short-acting beta$_2$ agonists Absolute results not reported	WMD 0.16 95% CI 0.09 to 0.23 P <0.001	○○○	ipratropium

Quality of life

Short-acting anticholinergic compared with short-acting beta$_2$ agonist Ipratropium seems modestly more effective than a short-acting beta$_2$ agonist at improving fatigue, emotion, and mastery components of the Chronic Respiratory Disease Questionnaire (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[44] Systematic review	1529 people 5 RCTs in this analysis	**Improvement in the fatigue component of the Chronic Respiratory Disease Questionnaire (CRQ) , 85 days of treatment** with ipratropium with short-acting beta$_2$ agonists Absolute results not reported	WMD 0.13 95% CI 0.02 to 0.23 P = 0.02	○○○	ipratropium
[44] Systematic review	1529 people 5 RCTs in this analysis	**Improvement in the emotion component of the CRQ , 85 days of treatment** with ipratropium with short-acting beta$_2$ agonists Absolute results not reported	WMD 0.17 95% CI 0.05 to 0.29 P = 0.006	○○○	ipratropium
[44] Systematic review	1529 people 5 RCTs in this analysis	**Improvement in the mastery component of the CRQ , 85 days of treatment** with ipratropium with short-acting beta$_2$ agonists Absolute results not reported	WMD 0.18 95% CI 0.06 to 0.30 P = 0.004	○○○	ipratropium

Mortality

No data from the following reference on this outcome. [44]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[44] Systematic review	1858 people 6 RCTs in this analysis	**Proportion of people reporting an adverse effect** 84/928 (9%) with ipratropium 111/930 (12%) with short-acting beta$_2$ agonists	RR 0.75 95% CI 0.57 to 0.97 P = 0.03 There was significant heterogeneity (I^2 = 60%) among studies in this analysis. The reason for the heterogeneity was not reported	●○○	ipratropium

Short-acting anticholinergic versus long-acting beta$_2$ agonist:

We found 5 systematic reviews comparing anticholinergics versus beta$_2$ agonists. [29] [48] [30] [44] [45] The reviews did not report data in terms of short- or long-term duration of treatment as defined in our Methods section, but by length of drug action. We report comparisons as reported in the reviews, and specify the duration of treatment where possible. One review compared anticholinergics as a class versus beta$_2$ agonists as a class (see further information on studies for results). [30] Two systematic reviews (search date 2006, 8 RCTs, 3713 people, [30] and search date 2008, 6 RCTs, 2604 people [45]) compared short-acting anticholinergics versus long-acting beta$_2$ agonists. Three RCTs were identified by both reviews. Both reviews included unpublished data obtained directly from drug companies. The reviews reported data on ipratropium versus salmeterol and ipratropium versus formoterol separately and reported on different outcomes.

Lung function and exercise capacity

Short-acting anticholinergic compared with long-acting beta$_2$ agonist Ipratropium seems less effective than salmeterol at improving FEV_1 at 12 weeks, but equally effective at improving the 6-minute walking distance test (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[45] Systematic review	458 people 2 RCTs in this analysis	**Change in FEV_1 from baseline , 12 weeks** with ipratropium with salmeterol Absolute results not reported	WMD –0.06 L 95% CI –0.11 L to 0 L P = 0.05 Difference between groups was of borderline significance	○○○	salmeterol
Exercise capacity					
[45] Systematic review	471 people 2 RCTs in this analysis	**Change in 6-minute walking distance , 12 weeks** with ipratropium with salmeterol Absolute results not reported	WMD +10.47 m 95% CI –1.24 m to +22.19 m P = 0.08	⟷	Not significant

COPD exacerbation and worsening of symptoms

Short-acting anticholinergic compared with long-acting beta$_2$ agonist Ipratropium and the long-acting beta$_2$ agonists salmeterol and formoterol seem equally effective at improving COPD exacerbations (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[30] Systematic review	538 people 2 RCTs in this analysis	**Risk of COPD exacerbation** with ipratropium with salmeterol Absolute results not reported	OR (salmeterol *v* ipratropium) 0.81 95% CI 0.56 to 1.19 P = 0.29	⟷	Not significant
[30] Systematic review	703 people 2 RCTs in this analysis The two RCTs were reported in three publications	**Risk of COPD exacerbation** with ipratropium with formoterol Absolute results not reported	OR (formoterol *v* ipratropium) 0.78 95% CI 0.44 to 1.37 P = 0.39	⟷	Not significant

Quality of life

Short-acting anticholinergic compared with long-acting beta$_2$ agonist Ipratropium and the long-acting beta$_2$ agonists salmeterol and formoterol seem equally effective at 12 weeks at improving total score on the Chronic Respiratory Disease Questionnaire (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[45] Systematic review	467 people 2 RCTs in this analysis	**Total improvement in the Chronic Respiratory Disease Questionnaire (CRQ) , 12 weeks** with ipratropium with salmeterol Absolute results not reported	WMD –0.58 95% CI –3.50 to +2.35 P = 0.7	⟷	Not significant

Mortality

No data from the following reference on this outcome. [30] [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] Systematic review	538 people 2 RCTs in this analysis	**Proportion of people withdrawing from a study because of adverse effects** with ipratropium with salmeterol Absolute results not reported	OR 0.45 95% CI 0.07 to 2.95 P = 0.40	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[30] Systematic review	703 people 2 RCTs in this analysis	**Proportion of people withdrawing from a study because of adverse effects** with ipratropium with formoterol Absolute results not reported	OR 1.84 95% CI 0.64 to 5.31 P = 0.26	⟷	Not significant
[45] Systematic review	1365 people 4 RCTs in this analysis	**Proportion of people withdrawing from a study because of adverse effects** 30/682 (4%) with ipratropium 21/683 (3%) with salmeterol	RR 1.42 95% CI 0.82 to 2.45 P = 0.2 Further details on types of adverse effect associated with treatments not reported	⟷	Not significant
[45] Systematic review	1365 people 4 RCTs in this analysis	**Proportion of people reporting an adverse effect** 365/682 (53.5%) with ipratropium 363/683 (53.1%) with salmeterol	RR 1.00 95% CI 0.91 to 1.10 P = 1 Further details on types of adverse effect associated with treatments not reported	⟷	Not significant

Long-acting anticholinergic versus short-acting beta$_2$ agonist:

We found no systematic review or RCTs. One review compared anticholinergics as a class versus beta$_2$ agonists as a class (see further information on studies for results). [30]

Long-acting anticholinergic versus long-acting beta$_2$ agonist:

We found 5 systematic reviews comparing anticholinergics versus beta$_2$ agonists. [29] [48] [30] [44] [45] The reviews did not report data in terms of short- or long-term duration of treatment as defined in our Methods section, but by length of drug action. We report comparisons as reported in the reviews, and specify the duration of treatment where possible. One review compared anticholinergics as a class versus beta$_2$ agonists as a class (see further information on studies for results). [30] Three systematic reviews compared long-acting anticholinergic versus long-acting beta$_2$ agonist. [29] [48] [30] There is some overlap in the RCTs identified by the reviews; however, no single RCT was identified by all three reviews. The reviews reported on different outcomes and different comparisons of long-acting anticholinergic versus long-acting beta$_2$ agonist.

Mortality

Long-acting anticholinergic compared with long-acting beta$_2$ agonist Tiotropium and salmeterol are equally effective at reducing all-cause mortality (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[48] Systematic review	1460 people 2 RCTs in this analysis	**All-cause mortality** 2/730 (0.2%) with tiotropium 6/730 (0.8%) with salmeterol	OR 0.38 95% CI 0.09 to 1.66 P = 0.20	⟷	Not significant

Lung function and exercise capacity

Long-acting anticholinergic compared with long-acting beta$_2$ agonist Tiotropium seems more effective than salmeterol at improving FEV$_1$ (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[48] Systematic review	1382 people 2 RCTs in this analysis	**Improvement in FEV_1** with tiotropium with salmeterol Absolute results not reported	WMD 28.97 95% CI 6.45 to 51.49 P = 0.01	○○○	tiotropium

COPD exacerbation and worsening of symptoms

Long-acting anticholinergic compared with long-acting beta$_2$ agonist Tiotropium and salmeterol are equally effective at improving COPD exacerbations (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbation					
[48] Systematic review	1460 people 2 RCTs in this analysis	**Proportion of people with an exacerbation of COPD** 159/730 (22%) with tiotropium 178/730 (24%) with salmeterol Two other reviews (search date 2002, 2 RCTs, 1830 people; [29] and search date 2006, 2 RCTs, 807 people [30]) found similar results for this comparison and outcome	OR 0.86 95% CI 0.67 to 1.11 P = 0.24	⟷	Not significant

Quality of life

Long-acting anticholinergic compared with long-acting beta$_2$ agonist Tiotropium and salmeterol seem equally effective at improving St George's Respiratory Questionnaire scores (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[30] Systematic review	807 people 2 RCTs in this analysis	**Improvement in St George's Respiratory Questionnaire score** with tiotropium with salmeterol Absolute results not reported	OR (salmeterol *v* tiotropium) 0.79 95% CI 0.60 to 1.05	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] Systematic review	807 people 2 RCTs in this analysis	**Proportion of people withdrawing from a study because of adverse effects** with tiotropium with salmeterol Absolute results not reported	OR (salmeterol *v* tiotropium) 2.16 95% CI 1.36 to 3.43 P = 0.001 No further information on adverse effects reported	●●○	tiotropium

No data from the following reference on this outcome. [29] [48]

Further information on studies

[30] The review compared anticholinergics as a class versus beta$_2$ agonists as a class. It found no significant difference between drug classes in mortality rate or risk of exacerbation of COPD (mortality [5 RCTs, 1925 people]: OR 4.36, 95% CI 0.73 to 25.93, P = 0.11; exacerbation of COPD [6 RCTs, 2048 people]: OR 0.94, 95% CI 0.76 to 1.17, P = 0.59; absolute numbers not reported). The review also found no significant difference between drug classes in proportion of people withdrawing from a trial because of adverse effects (OR 1.53, 95% CI 0.88 to 2.64; P = 0.13; absolute numbers not reported). The review also compared tiotropium versus formoterol (1 RCT, 74 people), but reported no data for this comparison.

Comment: It has been suggested that older people have a greater bronchodilator response with anticholinergic drugs than with beta$_2$ agonists, but we found no evidence for this.

OPTION THEOPHYLLINE

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Theophylline may improve lung function compared with placebo, but adverse effects limit its usefulness in stable COPD.
- Theophylline has a narrow therapeutic range and is associated with adverse effects such as diarrhoea, headache, irritability, seizures, and cardiac arrhythmias. The usefulness of theophyllines is limited by adverse effects and the need for frequent monitoring of blood concentrations.

Benefits and harms

Theophylline (short-term treatment) versus placebo:

We found two systematic reviews (search dates 2005 [49] [50]) and one small subsequent RCT. [51]

Lung function and exercise capacity

Compared with placebo Theophylline (short-term treatment) seems modestly more effective at improving FEV$_1$, but seems no more effective at improving maximum walking distance at 6 minutes (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[50] Systematic review	704 people with COPD 10 RCTs in this analysis	**Improvement in pre-dose FEV$_1$, 2 days to 12 months** with theophylline with placebo Absolute numbers not reported	WMD 0.108 L 95% CI 0.05 L to 0.16 L P <0.05	○○○	theophylline
[50] Systematic review	166 people with COPD 6 RCTs in this analysis	**Improvement in pre-dose FVC, 2 days to 12 months** with theophylline with placebo Absolute numbers not reported	WMD 0.186 L 95% CI 0.04 L to 0.34 L P <0.05	○○○	theophylline
[51] RCT	36 people with COPD	**Improvement in pre-dose FEV$_1$, 4 weeks** with oral theophylline 200 mg or 300 mg with placebo Absolute results reported graphically	P = 0.78	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Participants received tiotropium 18 micrograms daily plus formoterol 12 micrograms twice daily for 4 weeks, followed by additional oral theophylline 200 mg or 300 mg twice daily (depending on participant's weight) or placebo for a further 4 weeks			
[51] RCT	36 people with COPD	**Improvement in pre-dose FVC , 4 weeks** with oral theophylline 200 mg or 300 mg with placebo Absolute results reported graphically Participants received tiotropium 18 micrograms daily plus formoterol 12 micrograms twice daily for 4 weeks, followed by additional oral theophylline 200 mg or 300 mg twice daily (depending on participant's weight) or placebo for a further 4 weeks	P = 0.64	⟷	Not significant
Exercise capacity					
[49] Systematic review	58 people 2 RCTs in this analysis	**Maximum walking distance , 6 minutes** with theophylline with placebo Absolute results not reported	WMD +33.38 m 95% CI –11.44 m to +78.20 m	⟷	Not significant

Mortality

No data from the following reference on this outcome. [49] [50] [51]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [49] [50] [51]

Quality of life

No data from the following reference on this outcome. [49] [50] [51]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[49] Systematic review	39 people 3 RCTs in this analysis	**Nausea** with theophylline with placebo Absolute results not reported	RR 7.67 95% CI 1.47 to 39.94	●●●	placebo

No data from the following reference on this outcome. [50] [51]

Theophylline (long-term treatment) versus placebo:

We found two RCTs assessing the effects of theophylline compared with placebo in the long term. [52] [53]

Lung function and exercise capacity

Compared with placebo Theophylline (long-term treatment) may be more effective at improving FEV_1, including pre-bronchodilator FEV_1 but not post-bronchodilator FEV_1 (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[52] RCT **4-armed trial**	854 people The third and fourth arms assessed double-blinded formoterol 12 micrograms twice daily and formoterol 24 micrograms twice daily	**Mean difference in FEV_1 , 12 months** with theophylline (220 mg or 300 mg slow-release formulation) with placebo Absolute results not reported	Difference between groups: +120 mL (theophylline *v* placebo) CI not reported P <0.001 The theophylline arm was open label	○○○	theophylline
[53] RCT	110 people	**Mean change in pre-bronchodilator FEV_1 (change from baseline) , 12 months** +6.3 mL with theophylline (100 mg twice daily) –53.3 mL with placebo	P = 0.04	○○○	theophylline
[53] RCT	110 people	**Mean change in post-bronchodilator FEV_1 (change from baseline) , 12 months** –55.9 mL with theophylline (100 mg twice daily) –55.7 mL with placebo	P = 0.50	⟷	Not significant

COPD exacerbation and worsening of symptoms

Compared with placebo Theophylline (long-term treatment) seems more effective at 12 months at reducing the frequency and duration of acute COPD exacerbations (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations (frequency and duration)					
[53] RCT	110 people	**Frequency of acute COPD exacerbations (per year) , 12 months** 0.79 with theophylline (100 mg twice daily)	P = 0.047	○○○	theophylline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		1.70 with placebo			
[53] RCT	110 people	**Duration of acute COPD exacerbations (per year) , 12 months** 4.58 days with theophylline (100 mg twice daily) 12.47 days with placebo	P = 0.045	○○○	theophylline

No data from the following reference on this outcome. [52]

Mortality

No data from the following reference on this outcome. [52] [53]

Quality of life

No data from the following reference on this outcome. [52] [53]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[52] RCT **4-armed trial**	854 people The third and fourth arms assessed the effects of double-blinded formoterol 12 micrograms twice daily and formoterol 24 micrograms twice daily	**Discontinuation of treatment , 12 months** with theophylline (220 mg or 300 mg slow-release formulation) with placebo Absolute results not reported The RCT found that people receiving conventional-dose theophylline were twice as likely to discontinue treatment compared with those taking placebo	P <0.002 (theophylline *v* placebo) The theophylline arm was open label	○○○	placebo
[53] RCT	110 people	**Proportion of people reporting an adverse effect , 12 months** 10/57 (18%) with theophylline (100 mg twice daily) 3/53 (6%) with placebo Nausea and diarrhoea were the most frequently reported adverse effects	P = 0.076	⟷	Not significant

Further information on studies

[51] Six of 16 people (in a trial containing 36 people) had serum theophylline concentrations below the therapeutic threshold. This may have biased results toward placebo.

Comment: **Clinical guide:**
The therapeutic range for theophyllines is small, with blood concentrations of 10 mg/L to 15 mg/L required for optimal effects. Nausea and other adverse effects associated with the use of theophylline, such as diarrhoea, headache, irritability, seizures, and cardiac arrhythmias, may occur within the therapeutic range. [54] The usefulness of theophylline, especially when used in conventional doses, is limited by adverse effects associated with its use, and by the need for frequent monitoring of blood concentrations.

OPTION CORTICOSTEROIDS (ORAL)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Oral corticosteroids may improve short-term lung function, but have serious adverse effects.
- We found no direct information from RCTs about the effects of oral corticosteroids on decline in lung function in the long term.
- Long-term systemic corticosteroids are associated with serious adverse effects, including osteoporosis and diabetes.

Benefits and harms

Oral corticosteroids versus placebo:

We found one systematic review (search date 1989, 10 RCTs, 445 people), comparing oral corticosteroids versus placebo in people with stable COPD. [55] Treatment usually lasted 2 to 4 weeks. We found no RCTs examining the effects of oral corticosteroids in the long term on decline in lung function.

Lung function and exercise capacity

Compared with placebo Oral corticosteroids used in the short term for 2 to 4 weeks seem more effective at increasing the proportion of people with at least a 20% improvement in baseline FEV_1 in people with stable COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[55] Systematic review	445 people 10 RCTs in this analysis	**Proportion of people with at least a 20% improvement in baseline FEV_1** with oral corticosteroid with placebo Absolute results not reported	WMD 10% 95% CI 2% to 18% When 5 RCTs not meeting all quality criteria were included in the analysis, the difference in effect size was 11% (95% CI 4% to 18%)	◌◌◌	oral corticosteroid

Mortality

No data from the following reference on this outcome. [55]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [55]

Quality of life

No data from the following reference on this outcome. [55]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[56] Systematic review	Number of people not reported	**Adverse effects** with with Many reviews have described the considerable harms of systemic corticosteroids, including osteo-porosis and induction of diabetes			

Further information on studies

Comment: We found one narrative review of oral corticosteroids in patients with COPD, which focused on possible effects on bone mineral density of treatments for COPD including oral corticosteroids, but we do not discuss it here because it does not contribute further to the conclusions. [57]

OPTION CORTICOSTEROIDS (INHALED)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Inhaled corticosteroids reduce exacerbations in COPD and reduce decline in FEV_1, but the beneficial effects are small.
- Combined inhaled corticosteroids plus long-acting $beta_2$ agonists improve lung function and symptoms and reduce exacerbations compared with placebo, and may be more effective than either treatment alone.
- Long-term treatment with inhaled corticosteroids may predispose to adverse effects such as skin bruising, oral candidiasis, and pneumonia.

Benefits and harms

Inhaled corticosteroids (short-term treatment) versus placebo:

We found one systematic review (search date 2007). [58]

Lung function and exercise capacity

Compared with placebo Inhaled corticosteroids (short-term treatment) seems no more effective at improving FEV_1 in people with moderate to severe COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[58] Systematic review	424 people with COPD 5 RCTs in this analysis	**Change in pre-bronchodilator FEV_1 , 2 to 6 months** with inhaled corticosteroid with placebo Absolute numbers not reported	WMD 0.06 L 95% CI 0.03 to 0.09 P = 0.0002 A statistically significant, but modest effect	○○○	inhaled corticos-teroid

Mortality

No data from the following reference on this outcome. [58]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [58]

Quality of life

No data from the following reference on this outcome. [58]

Adverse effects

No data from the following reference on this outcome. [58]

Inhaled corticosteroids (long-term treatment) versus placebo:

We found 6 systematic reviews (search dates 2001, [59] 2002, [60] 2003, [29] 2007, [58] and 2008 [61] [62]), and 3 additional RCTs. [63] [64] [35]

Mortality

Compared with placebo Inhaled corticosteroids (long-term treatment) seem no more effective at reducing mortality at 3 years in people with moderate to severe COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[62] Systematic review	9223 people with COPD 5 RCTs in this analysis	**All-cause mortality , 12 months** 128/4636 (2.8%) with inhaled corticosteroids 148/4597 (3.2%) with placebo	RR 0.86 95% CI 0.68 to 1.09 P = 0.2	⟷	Not significant
[35] RCT	6184 people with COPD; 6112 people included in efficacy analysis	**Mortality , 3 years** 246/1534 (16%) with fluticasone (500 micrograms twice daily)	HR 1.06 (fluticasone *v* placebo) 95% CI 0.89 to 1.27	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial	The third and fourth arms assessed salmeterol 50 micrograms once daily plus fluticasone 500 micrograms twice daily and salmeterol alone (50 micrograms twice daily)	231/1524 (15%) with placebo 3096 people in analysis Analysis included people who had discontinued study medication	P = 0.53		

No data from the following reference on this outcome. [59] [60] [29] [58] [61] [63] [64]

Lung function and exercise capacity

Compared with placebo Inhaled corticosteroids (long-term treatment) seem more effective at improving FEV_1 in people with moderate to severe COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[58] Systematic review	2333 people with COPD 4 RCTs in this analysis	**Reduction in annual decline in FEV_1 , at least 2 years** with inhaled corticosteroids with placebo Absolute numbers not reported People without bronchodilator response or bronchial hyperresponsiveness	+5.8 mL/year 95% CI –0.28 mL/year to +11.9 mL/year P >0.05	⟷	Not significant
[63] RCT **4-armed trial**	691 people The third and fourth arms assessed combination treatment with inhaled corticosteroids plus long-acting $beta_2$ agonist, and inhaled $beta_2$ agonists alone	**Improvement in FEV_1 , 6 months** with fluticasone (500 micrograms) with placebo Absolute results not reported	Difference in FEV_1: 105 mL (fluticasone *v* placebo) P <0.05	○○○	fluticasone
[64] RCT **4-armed trial**	723 people The third and fourth arms assessed combination treatment with inhaled corticosteroids plus long-acting $beta_2$ agonist, and inhaled $beta_2$ agonists alone	**Increase in post-dose FEV_1 from baseline , 6 months** 147 mL with fluticasone 58 mL with placebo	P <0.05 (fluticasone *v* placebo)	○○○	fluticasone

No data from the following reference on this outcome. [59] [60] [29] [61] [62] [35]

COPD exacerbation and worsening of symptoms

Compared with placebo Inhaled corticosteroids (long-term treatment) seem more effective at improving dyspnoea and at reducing COPD exacerbations in people with moderate to severe COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[61] Systematic review	8164 people with COPD 11 RCTs in this analysis	**Risk of COPD exacerbation , 1 to 4.5 years** with inhaled corticosteroid with placebo Absolute numbers not reported	RR 0.82 95% CI 0.73 to 0.92 P <0.05 Sensitivity analysis suggested that there was benefit only in people with severe disease (FEV_1 <50%)	●○○	inhaled corticos-teroids
Symptom severity					
[63] RCT **4-armed trial**	691 people The third and fourth arms as-sessed combina-tion treatment with inhaled corticos-teroids plus long-acting $beta_2$ ago-nist, and inhaled $beta_2$ agonists alone	**Improvement in transitional dyspnoea index (TDI) , 6 months** with fluticasone (500 micrograms) with placebo Absolute results not reported	Difference in TDI 1.0 P <0.05	○○○	fluticasone
[64] RCT **4-armed trial**	723 people The third and fourth arms as-sessed combina-tion treatment with inhaled corticos-teroids plus long-acting $beta_2$ ago-nist, and inhaled $beta_2$ agonists alone	**Mean TDI score , 6 months** 1.7 with fluticasone 1.0 with placebo 363 people in this analysis	P = 0.057	⟷	Not significant

No data from the following reference on this outcome. [59] [60] [29] [58] [62] [35]

Quality of life

Compared with placebo Inhaled corticosteroids (long-term treatment) seem more effective at improving health-related quality of life in people with COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Health-related quality of life					
[58] Systematic review	2507 people with COPD 5 RCTs in this analysis	**Rate of change in St George's Respiratory Questionnaire (SGRQ) , per year** with inhaled corticosteroids with placebo Absolute numbers not reported Analysis in "long-term" studies, but long term not further specified	WMD –1.22 units/year 95% CI –1.83 units/year to –0.60 units/year P >0.05	⟷	Not significant
[64] RCT **4-armed trial**	723 people The third and fourth arms as-sessed combina-tion treatment with inhaled corticos-teroids plus long-acting $beta_2$ ago-nist, and inhaled	**Improvement in Chronic Respi-ratory Disease Questionnaire (CRQ) score from baseline , 6 months** 10.4 with fluticasone 5.0 with placebo 363 people in this analysis	P = 0.002	○○○	fluticasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	beta$_2$ agonists alone				

No data from the following reference on this outcome. [59] [60] [29] [61] [62] [63] [35]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[59] Systematic review	3976 people 9 RCTs in this analysis RCTs were of at least 6 months' duration	**Oropharyngeal candidiasis** with inhaled corticosteroids with placebo Absolute results not reported	RR 2.1 95% CI 1.5 to 3.1	●●○	placebo
[29] Systematic review	5562 people with stable moderate to severe COPD 6 RCTs in this analysis 5 RCTs were also identified by a review [59] with an earlier search date	**Oral thrush** with inhaled corticosteroids with placebo Absolute results not reported	RR 2.98 95% CI 2.09 to 4.26	●●○	placebo
[29] Systematic review	3772 people with stable moderate to severe COPD 4 RCTs in this analysis 5 RCTs were also identified by a review [59] with an earlier search date	**Dysphonia** with inhaled corticosteroids with placebo Absolute results not reported	RR 2.02 95% CI 1.43 to 2.83	●●○	placebo
[58] Systematic review	3864 people with stable, moderate to severe COPD 4 RCTs in this analysis	**Bruising** with inhaled corticosteroids with placebo Absolute numbers not reported	OR 1.86 95% CI 1.39 to 2.48 P <0.05	●○○	placebo
[29] Systematic review	1867 people with stable moderate to severe COPD 2 RCTs in this analysis 5 RCTs were also identified by a review [59] with an earlier search date	**Cataracts** with inhaled corticosteroids with placebo Absolute results not reported	RR 1.05 95% CI 0.84 to 1.31	⟷	Not significant
[29] Systematic review	972 people with stable moderate to severe COPD Data from 1 RCT 5 RCTs were also identified by a re-	**Reduction in bone mineral density (BMD) (femoral neck and lumbar spine) , over 3 to 4 years** with inhaled triamcinolone with placebo	Reduction in BMD in femoral neck with triamcinolone compared with placebo: 1.57% 95% CI 2.40% to 0.74% Reduction in BMD in lumbar spine with triamcinolone compared with placebo: 1.07%	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	view [59] with an earlier search date	Absolute results not reported	95% CI 1.86% to 0.28%		
[29] Systematic review	972 people with stable moderate to severe COPD Data from 1 RCT 5 RCTs were also identified by a review [59] with an earlier search date	**Excess risk of fractures , 3 years** with inhaled triamcinolone with placebo Absolute results not reported	RR 0.70 95% CI 0.36 to 1.37	⟷	Not significant
[62] Systematic review	8131 people with COPD In review [57] 3 RCTs in this analysis	**Fracture risk , 3 years** 195/4073 (4.8%) with inhaled corticosteroid 178/4058 (4.4%) with placebo Absolute numbers not reported	RR 1.09 95% CI 0.89 to 1.33 P = 0.4	⟷	Not significant
[60] Systematic review	Number of people and RCTs in analysis not reported Review identified 12 RCTs (5775 people with COPD) of at least 6 months' duration 7 RCTs were also identified by one review, [59] and 5 RCTs were identified by another review [29]	**Proportion of people withdrawing from study because of adverse effects , mean follow-up of 20 months** with inhaled corticosteroids with placebo Absolute results not reported	RR 0.92 95% CI 0.74 to 1.14	⟷	Not significant
[63] RCT **4-armed trial**	691 people The remaining arms assessed combination treatment with inhaled corticosteroids plus long-acting beta$_2$ agonist, and inhaled beta$_2$ agonists alone	**Oropharyngeal candidiasis , 6 months** 10% with fluticasone (500 micrograms) <1% with placebo Absolute numbers not reported	P value not reported		
[64] RCT **4-armed trial**	723 people The remaining arms assessed the effects of combination treatment with inhaled corticosteroids plus long-acting beta$_2$ agonists, and inhaled beta$_2$ agonists alone	**Rate of serious adverse effects , 6 months** 5% with fluticasone 5% with placebo Absolute numbers not reported Rates reported to be about 5%	P value not reported		
[64] RCT **4-armed trial**	723 people The remaining arms assessed combination treatment with inhaled corticosteroids plus long-acting beta$_2$ agonists, and inhaled beta$_2$ agonists alone	**Rate of adverse effects leading to withdrawal of treatment , 6 months** 5% with fluticasone 5% with placebo Absolute numbers not reported No further data reported	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[35] RCT **4-armed trial**	6184 people with COPD; 6112 people included in efficacy analysis The remaining arms assessed salmeterol 50 micrograms once daily plus fluticasone 500 micrograms twice daily and salmeterol alone (50 micrograms twice daily)	**Proportion of people experiencing a drug-related adverse effect , 3 years** 19% with fluticasone (500 micrograms twice daily) 13% with placebo Absolute numbers not reported 3096 people in analysis Analysis included people who had discontinued study medication The most common adverse effect reported was COPD exacerbation	Significance not assessed		

No data from the following reference on this outcome. [61]

Inhaled corticosteroids alone versus inhaled corticosteroids plus beta$_2$ agonists:

See option on inhaled corticosteroids plus beta$_2$ agonists, p 41 .

Further information on studies

[35] The RCT also carried out a last observation carried forward analysis for the outcome of FEV_1. However, the withdrawal rate from the RCT was high and the proportion of people followed up at 3 years for this outcome was 56% (851/1524) in the placebo group and 62% (947/1534) in the fluticasone alone group. These do not meet *Clinical Evidence* follow-up reporting criteria of 80%, and so these data are not reported here.

Comment: **Clinical guide:**
Many of the RCTs of inhaled corticosteroids have been done in people with moderate to severe COPD (FEV_1 <50% predicted) and hence apply only to that population. The lifetime risk of fractures in people who take corticosteroids for longer than 3 to 4 years is unknown. The Global Initiative on Obstructive Pulmonary Disease has therefore advocated the use of inhaled corticosteroids only in people with an FEV_1 <50% predicted, and frequent exacerbations (at least 3 exacerbations in the past 3 years). [1]

OPTION CORTICOSTEROIDS PLUS LONG-ACTING BETA2 AGONISTS (INHALED)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Combined inhaled corticosteroids plus long-acting beta$_2$ agonists improve lung function, symptoms, and health-related quality of life and reduce exacerbations compared with placebo, and may be more effective than either treatment alone.

Benefits and harms

Corticosteroid plus long-acting beta$_2$ agonist versus placebo:

We found one systematic review (search date 2007) [65] and three additional RCTs. [66] [67] [68]

Mortality

Compared with placebo Combined inhaled corticosteroids plus long-acting beta$_2$ agonists are more effective at reducing all-cause mortality in people with moderate to severe disease (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[65] Systematic review	5752 people with COPD 7 RCTs in this analysis	**Mortality , 6 months to 3 years** 209/2946 (7%) with inhaled corticosteroid plus long-acting beta$_2$ agonist 255/2806 (9%) with placebo Treatment group included fluticasone plus salmeterol and budesonide plus formoterol	OR 0.79 95% CI 0.65 to 0.96 P = 0.02	○○○	inhaled corticosteroid plus long-acting beta$_2$ agonist
[65] Systematic review	3057 people with COPD Data from 1 RCT	**Mortality , 3 years** 193/1533 (13%) with fluticasone plus salmeterol 231/1524 (15%) with placebo The review did not find mortality data at 3 years for budesonide plus salmeterol	HR 0.83 95% CI 0.68 to 1.00 P = 0.04	⟷	Not significant
[66] RCT **6-armed trial**	1704 people with COPD The remaining arms assessed budesonide and formoterol alone	**Mortality , 6 months** 3/277 (1.1%) with budesonide 160 micrograms plus formoterol 4.5 micrograms in one metered-dose inhaler twice daily 4/281 (1.4%) with budesonide 80 micrograms plus formoterol 4.5 micrograms in one metered-dose inhaler twice daily 0/287 (0.0%) with budesonide 160 micrograms plus formoterol 4.5 micrograms in separate metered-dose inhalers twice daily 1/300 (0.3%) with placebo 1145 people in this analysis The RCT reported that none of the deaths was considered to be related to the study medication	Significance not assessed		
[67] RCT	445 Chinese people with COPD	**Mortality , 6 months** 2/297 (0.7%) with salmeterol 50 micrograms plus fluticasone 500 micrograms 0/148 (0%) with placebo Participants were randomised in a 2:1 ratio	Significance not assessed		

No data from the following reference on this outcome. [68]

Lung function and exercise capacity

Compared with placebo An inhaled corticosteroid plus a long-acting beta$_2$ agonist seems more effective at improving pre-dose FEV_1 in people with moderate to severe COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[65] Systematic review	1420 people with COPD 5 RCTs in this analysis	**Improvement in pre-dose FEV_1 , up to 24 weeks** with fluticasone plus salmeterol with placebo	WMD 0.16 L 95% CI 0.14 L to 0.19 L P <0.00001	○○○	fluticasone plus salmeterol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported			
[65] Systematic review	923 people with COPD 2 RCTs in this analysis	**Improvement in FEV_1 from baseline , 12 months** with budesonide plus formoterol with placebo Absolute numbers not reported Meta-analysis used fixed-effects model	14.4% 95% CI 11.91% to 16.90% P <0.00001	○○○	budesonide plus formoterol
[68] RCT **3-armed trial**	224 people with COPD The remaining arm assessed fluticasone alone	**Increase in pre-dose FEV_1 percentage predicted , 4 weeks** 3.8% with fluticasone 500 micrograms plus salmeterol 50 micrograms twice daily 1.0% with placebo 137 people in this analysis People were randomised in a 2:2:1 ratio between the 2 treatment arms and placebo	P <0.05	○○○	fluticasone plus salmeterol
[66] RCT **6-armed trial**	1704 people with COPD The remaining arms assessed budesonide and formoterol alone	**Improvement in pre-dose FEV_1 , 6 months** 0.09 L with budesonide 160 micrograms plus formoterol 4.5 micrograms in one metered-dose inhaler twice daily 0.07 L with budesonide 80 micrograms plus formoterol 4.5 micrograms in one metered-dose inhaler twice daily 0.08 L with budesonide 160 micrograms plus formoterol 4.5 micrograms in separate metered-dose inhalers twice daily 0.01 L with placebo 1145 people in this analysis	P <0.05 for all treatment arms *v* placebo	○○○	budesonide plus formoterol
[67] RCT	445 Chinese people with COPD	**Improvement in pre-dose FEV_1 , 6 months** 177 mL with salmeterol 50 micrograms plus fluticasone 500 micrograms 8 mL with placebo Participants were randomised in a 2:1 ratio 180 mL, 95% CI 91 mL to 268 mL improvement with salmeterol plus fluticasone after adjusting for study centre, age, sex, smoking, and baseline	P <0.001 for adjusted result (180 mL)	○○○	salmeterol plus fluticasone

COPD exacerbation and worsening of symptoms

Compared with placebo An inhaled corticosteroid plus a long-acting $beta_2$ agonist is more effective at reducing COPD exacerbation rates in people with moderate to severe disease (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[65] Systematic review	4222 people with COPD 3 RCTs in this analysis	**Rate of exacerbations , 6 months to years** with fluticasone plus salmeterol with placebo Absolute numbers not reported	RR 0.74 95% CI 0.69 to 0.80 P <0.00001	●○○	fluticasone plus salmeterol
[65] Systematic review	913 people with COPD 2 RCTs in this analysis	**Rate of exacerbations , 12 months** with budesonide plus formoterol with placebo Absolute numbers not reported	RR 0.74 95% CI 0.62 to 0.88 P <0.0005	●○○	budesonide plus formoterol
[67] RCT	445 Chinese people with COPD	**Annualised exacerbation rate , 24 weeks** 0.81 with salmeterol 50 micrograms plus fluticasone 500 micrograms 1.35 with placebo	RR 0.61 95% CI 0.45 to 0.84 P = 0.002	○○○	salmeterol plus fluticasone
[68] RCT **3-armed trial**	224 people with COPD The remaining arm assessed fluticasone alone	**Number of COPD exacerbations (including withdrawals due to exacerbation) , 4 weeks** 9/92 (10%) with fluticasone 500 micrograms plus salmeterol 50 micrograms twice daily 13/45 (29%) with placebo 137 people in this analysis The RCT reported that all people who withdrew during the treatment phase did so because of COPD exacerbations People were randomised in a 2:2:1 ratio between the 2 treatment arms and placebo	Significance not assessed People who withdrew were analysed separately from those who did not, with trends favouring fluticasone plus salmeterol	○○○	

No data from the following reference on this outcome. [66]

Quality of life

Compared with placebo Corticosteroids plus long-acting beta$_2$ agonists seem more effective at improving health-related quality of life in people with moderate to severe disease (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Health-related quality of life					
[65] Systematic review	712 people with COPD 2 RCTs in this analysis	**Mean change from baseline in Chronic Respiratory Disease Questionnaire , 6 months** 10 with fluticasone plus salmeterol 5 with placebo	WMD 5.0 95% CI 2.48 to 7.52 P = 0.0001	○○○	fluticasone plus salmeterol
[65] Systematic review	3346 people with COPD 4 RCTs in this analysis	**Mean change in St George's Respiratory Questionnaire (SGRQ) , 6 months to 3 years** with fluticasone plus salmeterol with placebo	–2.9 units 95% CI –3.61 units to –2.18 units P <0.00001	○○○	fluticasone plus salmeterol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported			
[65] Systematic review	923 people with COPD 2 RCTs in this analysis	**Mean change in SGRQ , 12 months** with budesonide plus formoterol with placebo Absolute numbers not reported The review noted significant heterogeneity between studies	–6.06 units *v* placebo 95% CI –7.90 units to –4.22 units P <0.00001	○○○	budesonide plus formoterol
[68] RCT **3-armed trial**	224 people with COPD The remaining arm assessed fluticasone alone	**Change in SGRQ , 4 weeks** –2.4 with fluticasone 500 micrograms plus salmeterol 50 micrograms twice daily +1.5 with placebo 137 people in this analysis Randomisation 2:2:1 for active treatments and placebo	P <0.05	○○○	fluticasone plus salmeterol

No data from the following reference on this outcome. [66] [67]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[65] Systematic review	5493 people with COPD 8 RCTs in this analysis	**Any adverse effects , up to 3 years** 2215/2808 (78.9%) with fluticasone plus salmeterol 2116/2685 (78.8%) with placebo Pneumonia, candidiasis, nasopharyngitis, hoarseness, and upper respiratory tract infections occurred significantly more frequently with fluticasone plus salmeterol than with placebo (P <0.05 for all comparisons *v* placebo)	OR 1.1 for overall events 95% CI 0.96 to 1.27 P = 0.18	⟷	Not significant
[65] Systematic review	923 people with COPD 2 RCTs in this analysis	**Serious adverse effects , 12 months** 108/462 (23%) with budesonide plus formoterol 103/461 (22%) with placebo	OR 1.06 95% CI 0.78 to 1.45 P = 0.7	⟷	Not significant
[67] RCT	445 Chinese people with COPD	**Incidence of adverse effects , 6 months** 165/297 (56%) with salmeterol 50 micrograms plus fluticasone 500 micrograms 81/148 (55%) with placebo Participants were randomised in a 2:1 ratio	Significance not assessed		

No data from the following reference on this outcome. [66] [68]

Corticosteroid plus long-acting beta$_2$ agonist versus corticosteroid alone:

We found one systematic review (search date 2007) [69] and two subsequent RCTs. [68] [66]

Mortality

Corticosteroid plus long-acting beta$_2$ agonist compared with corticosteroid alone Fluticasone plus salmeterol is more effective at 3 years than fluticasone alone at reducing all-cause mortality in people with moderate to severe disease. However, we don't know how budesonide plus formeterol compares with budesonide alone (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[69] Systematic review	4061 people with COPD 3 RCTs in this analysis	**Mortality , 1 to 3 years** 196/2022 (10%) with fluticasone plus salmeterol 249/2029 (12%) with fluticasone The review noted that this result was dominated by the effect of 1 large study (the TORCH trial) [35]	OR 0.76 95% CI 0.62 to 0.93 P = 0.0072	●○○	fluticasone plus salmeterol
[69] Systematic review	917 people with COPD 3 RCTs in this analysis	**Mortality , 1 year** 11/462 (2.4%) with budesonide plus formoterol 11/455 (2.4%) with budesonide	OR 0.98 95% CI 0.42 to 2.29 P = 0.96	⟷	Not significant
[66] RCT **6-armed trial**	1704 people with COPD The remaining arms assessed formoterol alone and placebo	**Mortality , 6 months** 3/277 (1.1%) with budesonide 160 micrograms plus formoterol 4.5 micrograms in one metered-dose inhaler twice daily 4/281 (1.4%) with budesonide 80 micrograms plus formoterol 4.5 micrograms in one metered-dose inhaler twice daily 0/287 (0.0%) with budesonide 160 micrograms plus formoterol 4.5 micrograms in separate metered-dose inhalers twice daily 2/275 (0.7%) with budesonide 160 micrograms twice daily 1120 people in this analysis The RCT reported that none of the deaths was considered to be related to the study medication	Significance not assessed		

No data from the following reference on this outcome. [68]

Lung function and exercise capacity

Compared with corticosteroid alone An inhaled corticosteroid plus a long-acting beta$_2$ agonist seems more effective at improving pre-dose FEV_1 in people with moderate to severe COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[69] Systematic review	690 people with COPD 2 RCTs in this analysis	**Improvement in pre-dose FEV_1, 6 months** with fluticasone plus salmeterol with fluticasone Absolute numbers not reported	WMD 0.05 L 95% CI 0.02 L to 0.09 L P = 0.006	○○○	fluticasone plus salmeterol
[69] Systematic review	917 people with COPD 3 RCTs in this analysis	**Increase in FEV_1, mean difference between groups , 1 year** with budesonide plus formoterol with budesonide Absolute numbers not reported	10.17% 95% CI 7.71% to 12.62% Meta-analysis using fixed-effects model P <0.00001	○○○	budesonide plus formoterol
[68] RCT **3-armed trial**	224 people with COPD The remaining arm assessed placebo	**Increase in FEV_1 percentage predicted , 4 weeks** 3.8% with fluticasone 500 micrograms plus salmeterol 50 micrograms twice daily 1.6% with fluticasone 500 micrograms twice daily 179 people in this analysis	Significance not assessed	○○○	

No data from the following reference on this outcome. [66]

COPD exacerbation and worsening of symptoms

Compared with corticosteroid alone An inhaled corticosteroid plus a long-acting $beta_2$ agonist seems more effective at reducing COPD exacerbations in people with moderate to severe disease (moderate-quality of evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[69] Systematic review	4706 people with COPD 4 RCTs in this analysis	**Risk of COPD exacerbation , 1 to 3 years** with long-acting $beta_2$ agonist (LABA) plus corticosteroid with corticosteroid alone Absolute numbers not reported Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol	RR 0.91 95% CI 0.85 to 0.97 P = 0.0075	●○○	LABA
[68] RCT **3-armed trial**	224 people with COPD The remaining arm assessed placebo	**Number of COPD exacerbations (including withdrawals due to exacerbation) , 4 weeks** 9/92 (10%) with fluticasone 500 micrograms plus salmeterol 50 micrograms twice daily 6/87 (7%) with fluticasone 500 micrograms alone 179 people in this analysis The RCT reported that all people who withdrew during the treatment phase did so because of COPD exacerbations	Significance not assessed People who withdrew were analysed separately from those who did not, with trends favouring fluticasone		

No data from the following reference on this outcome. [66]

Quality of life

Compared with corticosteroid alone A corticosteroid plus a long-acting beta$_2$ agonist seems more effective at improving health-related quality of life in people with moderate to severe disease (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Health-related quality of life					
[69] Systematic review	696 people with COPD 2 RCTs in this analysis	**Mean change in Chronic Respiratory Disease Questionnaire (CRQ) , 6 months** with fluticasone plus salmeterol with fluticasone Absolute numbers not reported	WMD +2.34 95% CI –3.15 to +7.82 P = 0.4	⟷	Not significant
[69] Systematic review	3001 people with COPD 3 RCTs in this analysis	**Mean change in St George's Respiratory Questionnaire (SGRQ) , 1 to 3 years** with fluticasone plus salmeterol with fluticasone Absolute numbers not reported	WMD –1.3 95% CI –2.04 to –0.57 P <0.0005	○○○	fluticasone plus salmeterol
[69] Systematic review	917 people with COPD 2 RCTs in this analysis	**Mean change in SGRQ , 12 months** with budesonide plus formoterol with budesonide Absolute numbers not reported	WMD –3.26 95% CI –5.10 to –1.42 P = 0.0005	○○○	budesonide plus formoterol

No data from the following reference on this outcome. [68] [66]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[69] Systematic review	4795 people with COPD 5 RCTs in this analysis	**Proportion of people reporting an adverse effect , 6 months to 3 years** 1993/2382 (83.7%) with fluticasone plus salmeterol 2038/2413 (84.5%) with fluticasone alone	OR 0.94 95% CI 0.80 to 1.10 P = 0.41	⟷	Not significant
[69] Systematic review	5033 people with COPD 5 RCTs in this analysis	**Episodes of pneumonia , 6 months to 3 years** 224/2501 (9%) with long-acting beta$_2$ agonist (LABA) plus corticosteroid 202/2532 (8%) with fluticasone alone	OR 1.13 95% CI 0.92 to 1.38 P = 0.23	⟷	Not significant

No data from the following reference on this outcome. [68] [66]

Corticosteroid plus long-acting beta$_2$ agonist versus beta$_2$ agonist alone:

We found two systematic reviews (search dates 2009 [70] and 2007 [71]).

Mortality

Corticosteroid plus long-acting beta$_2$ agonist compared with long-acting beta$_2$ agonist alone Fluticasone plus salmeterol seems no more effective at 3 years than salmeterol alone at reducing all-cause mortality in people with moderate to severe disease (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[70] Systematic review	10,013 people with COPD 11 RCTs in this analysis	**All-cause mortality , 1 month to >12 months** 240/5292 (4.5%) with corticosteroid plus long-acting beta$_2$ agonist (LABA) 261/4721 (5.5%) with LABA Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	RR 0.90 95% CI 0.76 to 1.06 P value not reported; reported as not significant	⟷	Not significant

No data from the following reference on this outcome. [71]

Lung function and exercise capacity

Compared with long-acting beta$_2$ agonist alone An inhaled corticosteroid plus a long-acting beta$_2$ agonist may be more effective at improving pre-dose FEV_1 in people with moderate to severe COPD (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[70] Systematic review	10,695 people with COPD 13 RCTs in this analysis	**Increase in pre-dose FEV_1 , 1 month to >12 months** with corticosteroid plus long-acting beta$_2$ agonist (LABA) with LABA Absolute numbers not reported Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	WMD 0.06 L 95% CI 0.04 L to 0.07 L P = 0.0001	○○○	corticosteroid plus LABA

No data from the following reference on this outcome. [71]

COPD exacerbation and worsening of symptoms

Compared with long-acting beta$_2$ agonist alone An inhaled corticosteroid plus a long-acting beta$_2$ agonist may be more effective at reducing COPD exacerbations in people with moderate to severe disease (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[70] Systematic review	12,297 people with COPD 14 RCTs in this analysis	**Exacerbations requiring hospital admission or withdrawal , 1 month to >12 months** 757/6685 (11.3%) with corticosteroid plus long-acting beta$_2$ agonist (LABA) 704/5612 (12.5%) with LABA Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	RR 0.91 95% CI 0.82 to 1.01 P value not reported; reported as not significant	⟷	Not significant
[70] Systematic review	9590 people with COPD 11 RCTs in this analysis	**Exacerbations requiring systemic corticosteroids , 1 month to >12 months** 794/4532 (18%) with corticosteroid plus LABA 1015/5058 (20%) with LABA Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	RR 0.84 95% CI 0.74 to 0.96 P = 0.008	●○○	corticosteroid plus LABA

No data from the following reference on this outcome. [71]

Quality of life

Compared with long-acting beta$_2$ agonist alone A corticosteroid plus a long-acting beta$_2$ agonist may be more effective at improving health-related quality of life in people with moderate to severe disease (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Health-related quality of life					
[71] Systematic review	680 people with COPD 2 RCTs in this analysis	**Mean change in Chronic Respiratory Disease Questionnaire (CRQ) , 6 months** with fluticasone plus salmeterol with salmeterol alone Absolute results not reported	WMD 2.83 95% CI 0.25 to 5.41 P = 0.03	○○○	fluticasone plus salmeterol
[70] Systematic review	8657 people with COPD 8 RCTs in this analysis	**Mean change in St George's Respiratory Questionnaire , 1 month to >12 months** with corticosteroid plus long-acting beta$_2$ agonist (LABA) with LABA Absolute numbers not reported Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	WMD –1.88 95% CI –2.44 to –1.33 P = 0.0001	○○○	corticosteroid plus LABA

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[71] Systematic review	6671 people with COPD 7 RCTs in this analysis	**Proportion of people reporting any adverse effect , 6 months to 3 years** 2481/3338 (74.3%) with fluticasone plus salmeterol 2464/3333 (73.9%) with salmeterol alone	RR 1.02 95% CI 0.91 to 1.15 P = 0.72	⟷	Not significant
[70] Systematic review	9752 people with COPD 11 RCTs in this analysis	**Episodes of pneumonia , 1 month to >12 months** 263/5212 (5%) with LABA plus corticosteroid 153/4540 (3%) with LABA Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	RR 1.63 95% CI 1.35 to 1.98 P = 0.0001	●○○	LABA
[70] Systematic review	6262 people with COPD 8 RCTs in this analysis	**Oropharyngeal candidiasis , 1 month to >12 months** 292/3521 (8%) with LABA plus corticosteroid 200/2741 (7%) with LABA Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	RR 1.59 95% CI 1.07 to 2.37 P = 0.002	●○○	LABA
[70] Systematic review	9206 people with COPD 10 RCTs in this analysis	**Viral upper respiratory tract infections , 1 month to >12 months** 441/4844 (9%) with LABA plus corticosteroid 342/4362 (8%) with LABA Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	WMD RR 1.22 95% CI 1.07 to 1.39 P = 0.004	●○○	LABA
[70] Systematic review	6543 people with COPD 6 RCTs in this analysis	**MI , 1 month to >12 months** 34/3278 (1.0%) with LABA plus corticosteroid 33/3265 (1.0%) with LABA Pooled analysis of fluticasone plus salmeterol and budesonide plus formoterol The review noted that allocation concealment was adequate in only 5 of the 18 included RCTs	RR 1.03 95% CI 0.64 to 1.64 P = 0.91	⟷	Not significant

Further information on studies

Comment: **Clinical guide:**
The RCTs we found have been done mainly in people with moderate to severe disease (FEV_1 <50%) and hence apply to that population. The Global Initiative on Obstructive Pulmonary Disease has, therefore, advocated inhaled corticosteroids and the combination of inhaled corticosteroids plus long-acting $beta_2$ agonists only in people with FEV_1 <50% predicted and frequent exacerbations (i.e., at least 3 exacerbations in the past 3 years). [1]

OPTION MUCOLYTIC DRUGS

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- We don't know whether mucolytic drugs improve outcomes in people with COPD compared with placebo.

Benefits and harms

Mucolytics (long-term treatment) versus placebo:

We found two systematic reviews (search dates 2008 [72] and 1995 [73]). Not all people included in the reviews had COPD (see comment, below). We also found one subsequent RCT. [74]

COPD exacerbation and worsening of symptoms

Compared with placebo We don't know whether mucolytics (short-term treatment) are more effective at up to 36 months at reducing exacerbations in people with COPD (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[72] Systematic review	5055 people 23 RCTs in this analysis The review identified 6 RCTs in people with COPD and 20 RCTs in people with chronic bronchitis not further defined (total of 7335 people)	**Average number of exacerbations , 2 to 36 months** with mucolytics with placebo Absolute results not reported	WMD –0.05 exacerbations/month 95% CI –0.05 exacerbations/month to –0.04 exacerbations/month The results of the review should be interpreted with caution It was unclear how many people included in the review had COPD, and there was significant heterogeneity among the RCTs (symptom scores could not be pooled)	○○○	mucolytics
[73] Systematic review	Number of people not reported 9 RCTs in this analysis 8 RCTs were included in the first review [72]	**Average number of exacerbations , 3 to 24 months** with *N*-acetylcysteine with placebo Absolute results not reported	Overall weighted effect size 1.37 95% CI 1.25 to 1.50 Reduction 235 The result of the review should be interpreted with caution It was unclear how many people included in the review had COPD, and there was significant heterogeneity among the RCTs (symptom scores could not be pooled)	○○○	*N*-acetylcysteine
[74] RCT	709 Chinese people with COPD, with at least 2 exacerbations per year over 2 years	**Exacerbation risk , 12 months** 325 exacerbations in 354 people with carbocisteine 250 mg twice daily 439 exacerbations in 355 people with placebo	RR 0.75 95% CI 0.63 to 0.91 P = 0.04	●○○	carbocisteine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See further information on studies for baseline differences between groups			

Quality of life

Compared with placebo Mucolytics (long-term treatment) may be more effective at reducing days of disability at up to 36 months in people with COPD, but may be no more effective at improving St George's Respiratory Questionnaire scores at 12 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[72] Systematic review	1916 people 10 RCTs in this analysis The review identified 6 RCTs in people with COPD and 20 RCTs in people with chronic bronchitis not further defined (total of 7335 people)	**Days of disability , 2 to 36 months** with mucolytics with placebo Absolute results not reported	WMD –0.56 days/month 95% CI –0.77 days/months to –0.35 days/month The results of the review should be interpreted with caution It was unclear how many people included in the review had COPD, and there was significant heterogeneity among the RCTs (symptom scores could not be pooled)	○○○	mucolytics
[74] RCT	709 Chinese people with COPD, with at least 2 exacerbations per year over 2 years	**Change in St George's Respiratory Questionnaire (SGRQ) score , 12 months** –4.06 with carbocisteine 250 mg twice daily –0.05 with placebo See further information on studies for baseline differences between groups	P = 0.13	⟷	Not significant

No data from the following reference on this outcome. [73]

Mortality

No data from the following reference on this outcome. [72] [73] [74]

Lung function and exercise capacity

Mucolytics (long-term treatment) compared with placebo Carbocisteine may be no more effective than placebo at improving lung function in people with COPD (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[74] RCT	709 Chinese people with COPD, with at least 2 exacerbations per year over 2 years	**Lung function , 12 months** with carbocisteine 250 mg twice daily with placebo Absolute numbers not reported The RCT did not provide data but stated that there was no signifi-	P value not reported Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		cant difference between groups in post-bronchodilator FEV_1 or in SpO_2 See further information on studies for baseline differences between groups			

No data from the following reference on this outcome. [72] [73]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[72] Systematic review	4149 people 15 RCTs in this analysis The review identified 6 RCTs in people with COPD and 20 RCTs in people with chronic bronchitis not further defined (total of 7335 people)	**Proportion of people with an adverse effect , 2 to 36 months** 386/2074 (19%) with mucolytics 463/2075 (22%) with placebo	RR 0.84 95% CI 0.74 to 0.94 The results of the review should be interpreted with caution. The review reported that data from several large studies have been omitted from the meta-analysis It was unclear how many people included in the review had COPD, and there was significant heterogeneity among the RCTs (symptom scores could not be pooled)	●○○	mucolytics
[73] Systematic review	Number of people not reported 9 RCTs in this analysis 8 RCTs were included in the first review [72]	**Rate of adverse effects , 3 to 24 months** with *N*-acetylcysteine with placebo Absolute results not reported	Reported as not significant P value not reported The review reported that the adverse effects of *N*-acetylcysteine were mainly mild gastrointestinal (GI) complaints; no further information on adverse effects given The result of the review should be interpreted with caution It was unclear how many people included in the review had COPD, and there was significant heterogeneity among the RCTs (symptom scores could not be pooled)	⟷	Not significant
[74] RCT	709 Chinese people with COPD, with at least 2 exacerbations per year over 2 years	**Adverse effects , 12 months** 57/354 (16.1%) with carbocisteine 250 mg twice daily 56/355 (15.8%) with placebo The most common adverse effects were GI problems (14 with carbocisteine and 5 with placebo) and cardiac problems (9 with carbocisteine and 5 with placebo) See further information on studies for baseline differences between groups	Significance not assessed		

Further information on studies

[74] Less than one third of the people in the RCT were taking inhaled corticosteroids, anticholinergics, beta$_2$ agonists, or xanthines at baseline. There was also a trend towards more use of each class of medication at baseline in the treatment group. These factors may have biased the results in favour of carbocisteine.

Comment: One large RCT (523 people) identified by the reviews included people with only smoking-related COPD. [75] The RCT found no significant difference in FEV_1 decline and exacerbations between *N*-acetylcysteine 600 mg daily and placebo at 3 years (difference in yearly decline in FEV_1: 8 mL, 95% CI –25 mL to +10 mL; exacerbations/year: 1.25 with *N*-acetylcysteine *v* 1.29 with placebo; HR 0.99, 95% CI 0.89 to 1.10). However, pre-specified subgroup analysis was done for people who did or did not use inhaled corticosteroids at entry. The RCT found that *N*-acetylcysteine reduced exacerbations in people who did not take inhaled corticosteroids compared with placebo (155 people; HR 0.79, 95% CI 0.63 to 0.99).

Clinical guide:
The relative effects of mucolytics cannot be determined based on the current evidence, and so a direct comparison is required.

OPTION ANTIBIOTICS (PROPHYLACTIC)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- We don't know whether prophylactic antibiotics improve outcomes in people with COPD compared with placebo.

Benefits and harms

Prophylactic antibiotics versus placebo:

We found no systematic review or RCTs assessing the effects of prophylactic antibiotics in the short term. We found one systematic review (search date not reported, 9 RCTs, 1055 people; all trials performed before 1970; see comment below) comparing prophylactic antibiotics (tetracycline, penicillin, trimethoprim, sulfadimidine, and sulfaphenazole) versus placebo in people with COPD or chronic bronchitis in RCTs of duration from 3 months to 5 years. [76] We also found one subsequent RCT comparing erythromycin versus placebo. [77]

COPD exacerbation and worsening of symptoms

Compared with placebo We don't know whether prophylactic antibiotics are more effective at reducing exacerbations in people with COPD (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
COPD exacerbations					
[76] Systematic review	746 people 10 RCTs in this analysis	**Proportion of people with an exacerbation** 269/382 (70%) with prophylactic antibiotics 285/364 (78%) with placebo	RR 0.91 95% CI 0.84 to 0.99 The results of the review should be interpreted with caution (see comment)	●○○	prophylactic antibiotics
[76] Systematic review	779 people 8 RCTs in this analysis	**Number of exacerbations per person per year** with prophylactic antibiotics with placebo Absolute results not reported	WMD –0.15 95% CI –0.34 to +0.04 The results of the review should be interpreted with caution (see comment)	⟷	Not significant
[77] RCT	109 people with COPD, FEV_1 30% to 70% expected	**Number of moderate to severe exacerbations , 12 months** 81 exacerbations in 53 people with erythromycin 250 mg twice daily 125 exacerbations in 56 people with placebo	RR 0.65 95% CI 0.49 to 0.86 P = 0.003	●○○	prophylactic antibiotics

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See further information on studies for details of possible drug–drug interactions in this RCT			

Quality of life

Compared with placebo We don't know whether prophylactic antibiotics are more effective at reducing the number of days of disability per person per month treated in people with COPD (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Days of disability					
[76] Systematic review	755 people 7 RCTs in this analysis	**Number of days of disability per person per month treated** with prophylactic antibiotics with placebo Absolute results not reported	WMD –0.95 95% CI –1.89 to –0.01 (22% reduction) The results of the review should be interpreted with caution (see comment)	○○○	prophylactic antibiotics

No data from the following reference on this outcome. [77]

Mortality

No data from the following reference on this outcome. [76] [77]

Lung function and exercise capacity

Compared with placebo We don't know whether prophylactic antibiotics are more effective at maintaining lung function (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[77] RCT	109 outpatients with COPD, FEV_1 30% to 70% expected	**Decline in FEV_1 from baseline, 12 months** 0.12 L (from 1.25 L to 1.13 L) with erythromycin 250 mg twice daily 0.08 L (from 1.33 L to 1.25 L with placebo Analysis by linear mixed model See further information on studies for details of possible drug–drug interactions in this RCT	P = 0.97	⟷	Not significant

No data from the following reference on this outcome. [76]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[76] Systematic review	934 people 10 RCTs in this analysis	**Number of adverse effects** with prophylactic antibiotics with placebo Absolute results not reported In general, there was a poor reporting of possible adverse effects in most trials	Mean difference per person per year treated: 0.01 95% CI 0 to 0.02	○○○	placebo
[77] RCT	109 outpatients with COPD, FEV_1 30% to 70% expected	**Proportion of people with adverse effects , 12 months** 14/53 (26%) with erythromycin 250 mg twice daily 12/56 (21%) with placebo The main adverse effects were upper and lower gastrointestinal adverse effects, and rash. There were no significant differences between groups in any adverse effect	P >0.05	⟷	Not significant

Further information on studies

[77] The results of this RCT should be interpreted with caution as the effect may have been mediated by drug interactions with medications such as fluticasone or salmeterol rather than by antibiotic or direct anti-inflammatory effect.

Comment: **Clinical guide:**
The results of the review should be interpreted with caution. [76] It was unclear from the descriptions of the original studies how many participants had COPD (rather than chronic bronchitis without obstruction). Additionally, the data in the review are >30 years old, so the pathogens and the pattern of antibiotic sensitivity may have changed, and there is currently a wider range of antibiotics in use. Most people believe that prophylactic antibiotics do not have a place in routine treatment because of concerns about the development of antibiotic resistance and the possibility of adverse effects.

OPTION OXYGEN TREATMENT (LONG-TERM DOMICILIARY TREATMENT)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Long-term domiciliary oxygen treatment may improve survival in people with severe daytime hypoxaemia.

Benefits and harms

Oxygen compared with no oxygen (short-term treatment):

We found no systematic review or RCTs.

Oxygen versus no oxygen (long-term treatment):

We found one systematic review (search date 2007, 6 RCTs). [78] The review did not pool data for many outcomes because of differences in trial design and participant selection. The review identified one RCT in people with severe daytime hypoxaemia (arterial oxygen tension [PaO_2] 5.3–8.0 kPa). [79]

Mortality

Long-term treatment with oxygen compared with no oxygen Daily domiciliary oxygen supplementation seems more effective at reducing mortality at 5 years in people with severe daytime hypoxaemia but not in people with mild to moderate hypoxaemia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[78] Systematic review	87 people with severe daytime hypoxaemia Data from 1 RCT	**Mortality , 5 years** 19/42 (45%) with domiciliary daily oxygen supplementation 30/45 (67%) with no oxygen supplementation Domiciliary daily oxygen supplementation was given for at least 15 hours	RR 0.68 95% CI 0.46 to 1.00	●○○	domiciliary daily oxygen supplementation
[78] Systematic review	163 people with mild to moderate hypoxaemia (PaO_2 56–65 mmHg or >55 mmHg) 2 RCTs in this analysis	**Mortality , 36 to 85 months** 42/82 (51%) with domiciliary daily oxygen supplementation 35/81 (43%) with no oxygen supplementation	RR 1.18 95% CI 0.86 to 1.63	⟷	Not significant

Lung function and exercise capacity

Long-term treatment with oxygen compared with no oxygen Daily domiciliary oxygen supplementation seems no more effective at improving endurance time at 12 months in people with mild to moderate hypoxaemia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exercise capacity					
[78] Systematic review	28 people with mild to moderate hypoxaemia Data from 1 RCT	**Change in endurance time , 12 months** +7.1 minutes with domiciliary daily oxygen supplementation +4.9 minutes with no oxygen supplementation	WMD +2.20 minutes 95% CI –0.73 minutes to +5.13 minutes	⟷	Not significant

COPD exacerbation and worsening of symptoms

Long-term treatment with oxygen compared with no oxygen Daily domiciliary oxygen supplementation seems no more effective at improving dyspnoea scores at 12 months in people with mild to moderate hypoxaemia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[78] Systematic review	28 people with mild to moderate hypoxaemia Data from 1 RCT	**Dyspnoea score (assessed using Borg scale) , 12 months** +4.5 with domiciliary daily oxygen supplementation +5.7 with no oxygen supplementation	WMD –1.20 95% CI –2.47 to +0.07	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [78]

Adverse effects

No data from the following reference on this outcome. [78]

Further information on studies

[78] Only one of the RCTs identified by the review was double blinded.

[78] [80] One RCT (203 people, PaO_2 <7.4 kPa) identified by the review compared continuous *v* nocturnal domiciliary oxygen treatment. Continuous oxygen was associated with a significant reduction in mortality over 24 months (OR 0.45, 95% CI 0.25 to 0.81).

Comment: **Clinical guide:**
Domiciliary oxygen treatment seems to be more effective in people with severe hypoxaemia (PaO_2 <8.0 kPa) than in people with moderate hypoxaemia (conflicting findings among the studies) or those who have arterial desaturation only at night.

OPTION ALPHA1 ANTITRYPSIN

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- We don't know whether alpha$_1$ antitrypsin improves outcomes in people with COPD compared with placebo.
- We found insufficient information from a single RCT assessing alpha$_1$ antitrypsin in the short-term treatment of people with COPD.

Benefits and harms

Alpha$_1$ antitrypsin versus placebo (short-term treatment):

We found no systematic review or RCTs.

Alpha$_1$ antitrypsin versus placebo (long-term treatment):

We found one systematic review (search date 2007), [81] which included one RCT. [82] The review [81] also identified several observational studies (see comment).

Lung function and exercise capacity

Compared with placebo We don't know whether long-term treatment with alpha$_1$ antitrypsin is more effective at improving FEV_1 at 3 years in people with moderate emphysema (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[82] RCT	56 people with alpha$_1$ antitrypsin deficiency and moderate emphysema, FEV_1 30% to 80% predicted In review [81]	**Decline in FEV_1 , 1 year** 59 mL with alpha$_1$ antitrypsin infusions 250 mg/kg 79 mL with placebo (albumin) infusions Infusions were given monthly for at least 3 years	P = 0.25	⟷	Not significant

Mortality

No data from the following reference on this outcome. [81]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [81]

Quality of life

No data from the following reference on this outcome. [81]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[82] RCT	56 people with alpha$_1$ antitrypsin deficiency and moderate emphysema, FEV$_1$ 30% to 80% predicted In review [81]	**Adverse effects** with alpha$_1$ antitrypsin infusions 250 mg/kg with placebo (albumin) infusions Absolute results not reported Infusions were given monthly for at least 3 years The RCT reported no adverse effects in people taking alpha$_1$ antitrypsin or placebo			

Further information on studies

Comment: Observational studies identified in the systematic review [81] did not provide clear evidence of the effect of alpha$_1$ antitrypsin. For example, one cohort study (1048 people either homozygous for alpha$_1$ antitrypsin deficiency or with an alpha$_1$ antitrypsin concentration 11 micromol/L or less, with mean FEV$_1$ 49% ± 30% predicted) compared weekly infusions of alpha$_1$ antitrypsin 60 mg/kg versus placebo for 3.5 to 7.0 years. It found that alpha$_1$ antitrypsin significantly reduced mortality after an average of 5 years (RR of death 0.64, 95% CI 0.43 to 0.94). It found no significant difference between treatments in the decline in FEV$_1$, but in a subgroup of people with a mean FEV$_1$ of 35% to 49% predicted, alpha$_1$ antitrypsin significantly reduced the decline in FEV$_1$ (mean difference in FEV$_1$ 27 mL/year, 95% CI 3 mL/year to 51 mL/year; P = 0.03). A second cohort study (295 people homozygous for alpha$_1$ antitrypsin deficiency with FEV$_1$ below 65% predicted) compared 198 people who received weekly infusions of alpha$_1$ antitrypsin 60 mg/kg (duration not reported) versus 97 people who had never received alpha$_1$ antitrypsin. It found that alpha$_1$ antitrypsin significantly reduced the decline in FEV$_1$ (50 mL/year with alpha$_1$ antitrypsin *v* 80 mL/year with no alpha$_1$ antitrypsin; 95% CI not reported; P = 0.02). [81]

QUESTION What are the effects of smoking cessation interventions in people with stable COPD?

OPTION PSYCHOSOCIAL INTERVENTIONS ALONE FOR SMOKING CESSATION

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Psychosocial interventions alone for smoking cessation in people with COPD may reduce the decline in FEV_1 in people with signs of early COPD.

Benefits and harms

Psychosocial interventions versus usual care:

We found two systematic reviews (search dates 2007 [83] and 2002 [84]), which identified one three-armed RCT assessing the effects of a psychosocial intervention. [10]

Mortality

Smoking cessation interventions with and without ipratropium compared with usual care A psychosocial smoking cessation intervention alone seems no more effective at reducing all-cause mortality at 5 years in people with signs of early COPD, but smoking cessation interventions with and without ipratropium seem more effective at reducing all-cause mortality at 14.5 years (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[85] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day Further report of reference [10] The third arm assessed smoking cessation intervention plus ipratropium See further information on studies for full description of smoking intervention programme [86]	**All-cause mortality , 5 years** 44/1962 (2%) with smoking cessation intervention plus placebo 51/1964 (3%) with usual care 3926 people in this analysis	P = 0.47 (smoking cessation intervention plus placebo *v* usual care)	⟷	Not significant
[87] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**All-cause mortality , 14.5 years** 8.83/1000 person-years with smoking cessation intervention with or without ipratropium 10.83/1000 person-years with usual care	HR for mortality 1.18 95% CI 1.02 to 1.37 Combined analysis of smoking cessation programme with and without ipratropium (by intention-to-treat analysis) *v* usual care	●○○	smoking cessation intervention with or without ipratropium

Lung function and exercise capacity

Smoking cessation programme with or without ipratropium compared with usual care A psychosocial smoking cessation programme alone seems more effective at reducing the decline in FEV_1 at 1 to 5 years in people with signs of early COPD, and a psychosocial smoking cessation programme with or without ipratropium seems more effective at reducing the decline in FEV_1 at 11 years (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[10] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] The third arm assessed smoking cessation intervention plus ipratropium See further information on studies for full description of smoking intervention programme [86]	**Change in FEV_1 , 1 year** +11.2 mL with smoking cessation programme –34.3 mL with usual care 3926 people in this analysis	P <0.005 (smoking cessation programme *v* usual care)	○○○	smoking cessation intervention
[10] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] The third arm assessed the effects of smoking cessation intervention plus ipratropium See further information on studies for full description of smoking intervention programme [86]	**Change in FEV_1 , 5 years** –208 mL with smoking cessation programme –267 mL with usual care 3926 people in this analysis	P = 0.002 or less (smoking cessation programme *v* usual care) Results from completer analysis (about 90% of people)	○○○	smoking cessation intervention
[88] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] The third arm assessed the effects of smoking cessation intervention plus placebo	**Decline in FEV_1 (change from baseline) , 11 years** –502 mL with smoking cessation intervention with or without ipratropium +587 mL with usual care	P = 0.001 Combined analysis of smoking cessation programme with or without ipratropium *v* usual care	○○○	smoking cessation intervention with or without ipratropium

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	See further information on studies for full description of smoking intervention programme [86]				

COPD exacerbation and worsening of symptoms

Smoking cessation interventions with or without ipratropium compared with usual care Smoking cessation interventions with or without ipratropium seem more effective at reducing cough, phlegm, wheezing, and dyspnoea at 5 years in people with signs of early COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptoms					
[89] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD, mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Proportion of people with cough for at least 3 months/year , 5 years** 15% with smoking cessation intervention with or without ipratropium 23% with usual care Absolute numbers not reported	P <0.0001 Combined analysis of smoking cessation programme with and without ipratropium (by intention-to-treat [ITT] analysis) *v* usual care	○○○	smoking cessation intervention with or without ipratropium
[89] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Proportion of people with phlegm for at least 3 months/year , 5 years** 12% with smoking cessation intervention with or without ipratropium 20% with usual care Absolute numbers not reported	P <0.0001 Combined analysis of smoking cessation programme with and without ipratropium (by ITT analysis) *v* usual care	○○○	smoking cessation intervention with or without ipratropium
[89] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Proportion of people with wheezing , 5 years** 25% with smoking cessation intervention with or without ipratropium 31% with usual care Absolute numbers not reported	P <0.0001 Combined analysis of smoking cessation programme with and without ipratropium (by ITT analysis) *v* usual care	○○○	smoking cessation intervention with or without ipratropium

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[89] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Proportion of people with dyspnoea , 5 years** 19% with smoking cessation intervention with or without ipratropium 24% with usual care Absolute numbers not reported	P <0.0001 Combined analysis of smoking cessation programme with and without ipratropium (by ITT analysis) *v* usual care	○○○	smoking cessation intervention with or without ipratropium

No data from the following reference on this outcome. [10]

Quality of life

No data from the following reference on this outcome. [10] [83] [89]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] [90] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Adverse effects** with smoking cessation with or without ipratropium with usual care The RCT reported that 31% (about 1216 people) were still using nicotine gum after 1 year About 25% reported at least 1 adverse effect, but most were minor and transient. The most common adverse effects were: indigestion (5% for men and 4% for women), mouth irritation (6.2% for men and 6.5% for women), mouth ulcers (4% for men and 5% for women), nausea (2% for men and 4% for women), and hiccups (3% for men and 4% for women)			
[91] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83]	**Weight gain , 1 year** 2.61 kg for men, 2.63 kg for women with smoking cessation with or without ipratropium 0.61 kg for men, 1.10 kg for women with usual care	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	See further information on studies for full description of smoking intervention programme [86]				
[91] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Weight gain , 5 years** 3.9 kg for men, 4.75 kg for women with smoking cessation with or without ipratropium 2.6 kg for men, 2.84 kg for women with usual care	Significance not assessed		

Psychosocial intervention alone versus psychosocial intervention plus pharmacological treatment:
See option on psychosocial intervention plus pharmacological treatment for smoking cessation, p 66 .

Further information on studies

[86] The smoking cessation intervention consisted of an intensive 12-session smoking cessation programme combining behaviour modification and use of nicotine gum (nicotine polacrilex 2 mg) with a continuing 5-year maintenance programme that included monitoring of weight gain and nutritional counselling.

Comment: Despite the extensive literature on smoking cessation, we found only one RCT that assessed psychosocial interventions alone, and found no RCTs solely in people with COPD: most RCTs focused on combinations of interventions, continuous abstinence or point prevalence rates of smoking cessation as single outcome measures, and populations including either healthy people or healthy people and people with disease.

OPTION PHARMACOLOGICAL INTERVENTIONS ALONE FOR SMOKING CESSATION

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Combined psychosocial and pharmacological interventions for smoking cessation can slow the deterioration of lung function, but have not been shown to reduce long-term mortality compared with usual care.
- We found no direct information from RCTs about the effects of pharmacological interventions alone for smoking cessation in people with COPD.

Benefits and harms

Pharmacological interventions alone for smoking cessation:

We found one systematic review (search date 2002). [84] It found no RCTs examining the effects of pharmacological smoking cessation interventions alone for the outcomes of interest in this review (FEV_1 , peak expiratory flow, exacerbations, dyspnoea score, quality of life, or survival) specifically in people with COPD. The review [84] identified two RCTs, both of which examined pharmacological interventions plus psychosocial interventions (see option on psychosocial plus pharmacological interventions, p 66). [10] [92]

Further information on studies

Comment: One systematic review (search date 2001, 157 studies) assessed the effectiveness of bupropion and nicotine replacement treatment for smoking cessation, but did not focus solely on people with COPD. [93] [94] It found a low incidence of adverse events with nicotine replacement therapy, irrespective of the type of replacement. The most common adverse effects were localised reactions: skin sensitivity and irritation (with patches); throat irritation, nasal irritation, and runny nose (with nasal spray); hiccups, burning and smarting sensation in the mouth, sore throat, coughing, dry lips, and mouth ulcers (with nicotine sublingual tablets); and hiccups, gastrointestinal disturbances, jaw pain, and orodental problems (with nicotine gum). Sleep disturbances and alteration of mood may arise because of nicotine withdrawal. A small number of studies were done in specific subgroups (including smokers with lung disease). Results for individual subgroups were generally non-significant, but their direction was consistent with the overall pooled results. The systematic review did not report results separately in people with COPD. Regarding the safety of bupropion, the review concluded that seizure is the most significant and important potential adverse effect. However, this review did not identify RCTs that reported any seizures. Common adverse events of bupropion are: rash, pruritus, urticaria, irritability, insomnia, dry mouth, headache, and tremor. The adverse-effect profile of slow-release bupropion seems better than that of immediate-release bupropion. The results for specific subgroups (including smokers with pulmonary disease) were generally consistent with the overall pooled results, although results in people with COPD were not reported separately.

OPTION PSYCHOSOCIAL PLUS PHARMACOLOGICAL INTERVENTIONS FOR SMOKING CESSATION

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Combined psychosocial and pharmacological interventions for smoking cessation can slow the deterioration of lung function, but have not been shown to reduce long-term mortality compared with usual care.

Benefits and harms

Psychosocial plus pharmacological interventions versus usual care:

We found one systematic review (search date 2002), [83] which identified two RCTs examining psychosocial plus pharmacological interventions compared with usual care in people with COPD. [10] [92] One RCT reported only abstinence rates and adverse effects. [92] This study did not provide data about the effects on FEV_1 changes, peak expiratory flow, exacerbations, dyspnoea score, quality of life, or survival.

Mortality

Psychosocial plus pharmacological interventions compared with usual care Smoking cessation interventions with and without ipratropium seem more effective at 14.5 years but not at 5 years at reducing all-cause mortality in people with signs of early COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[85] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD, mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day Further report of reference [10]	**All-cause mortality , 5 years** 54/1961 (2.7%) with smoking cessation intervention plus ipratropium 51/1964 (2.6%) with usual care 3925 people in this analysis	P = 0.765 (smoking cessation intervention plus ipratropium *v* usual care)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The third arm assessed smoking cessation intervention plus placebo See further information on studies for full description of smoking intervention programme as reported in [86]				
[87] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme as reported in [86]	**All-cause mortality , 14.5 years** 8.83/1000 person-years with smoking cessation intervention with or without ipratropium 10.83/1000 person-years with usual care	HR for mortality 1.18 95% CI 1.02 to 1.37 Combined analysis of smoking cessation programme with and without ipratropium (by intention-to-treat analysis) *v* usual care	●○○	smoking cessation intervention with or without ipratropium

Lung function and exercise capacity

Psychosocial plus pharmacological interventions compared with usual care A psychosocial smoking cessation programme with or without ipratropium seems more effective at reducing the decline in FEV_1 at 1 to 11 years in people with signs of early COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[10] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] The third arm assessed the effects of smoking cessation intervention plus placebo See further information on studies for full description of smoking intervention programme [86]	**Change in FEV_1 , 1 year** +38.8 mL with smoking cessation intervention plus ipratropium –34.3 mL with usual care	P <0.005 (smoking cessation intervention plus ipratropium *v* usual care)	○○○	smoking cessation intervention plus ipratropium
[10] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30	**Change in FEV_1 , 5 years** –184 mL with smoking cessation intervention plus ipratropium –267 mL with usual care	P = 0.002 or less (smoking cessation intervention plus ipratropium *v* usual care) Results from completer analysis (about 90% of people)	○○○	smoking cessation intervention plus ipratropium

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	cigarettes smoked/day In review [83] The third arm assessed smoking cessation intervention plus placebo See further information on studies for full description of smoking intervention programme [86]				
[88] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] The third arm assessed the effects of smoking cessation intervention plus placebo See further information on studies for full description of smoking intervention programme [86]	**Decline in FEV_1 (change from baseline) , 11 years** –502 mL with smoking cessation intervention with or without ipratropium +587 mL with usual care	P = 0.001 Combined analysis of smoking cessation programme with or without ipratropium *v* usual care	○○○	smoking cessation intervention with or without ipratropium

COPD exacerbation and worsening of symptoms

Smoking cessation interventions with or without ipratropium compared with usual care Smoking cessation interventions with or without ipratropium seem more effective at reducing cough, phlegm, wheezing, and dyspnoea at 5 years in people with signs of early COPD (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptoms					
[89] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Proportion of people with cough for at least 3 months/year , 5 years** 15% with smoking cessation intervention with or without ipratropium 23% with usual care Absolute numbers not reported	P <0.0001 Combined analysis of smoking cessation programme with and without ipratropium (by intention-to-treat [ITT] analysis) *v* usual care	○○○	smoking cessation intervention with or without ipratropium
[89] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of ear-	**Proportion of people with phlegm for at least 3 months/year , 5 years**	P <0.0001 Combined analysis of smoking cessation programme with and without ipratropium (by ITT analysis) *v* usual care	○○○	smoking cessation intervention with or without ipratropium

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	ly COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	12% with smoking cessation intervention with or without ipratropium 20% with usual care Absolute numbers not reported			
[89] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Proportion of people with wheezing , 5 years** 25% with smoking cessation intervention with or without ipratropium 31% with usual care Absolute numbers not reported	P <0.0001 Combined analysis of smoking cessation programme with and without ipratropium (by ITT analysis) *v* usual care	○○○	smoking cessation intervention with or without ipratropium
[89] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Proportion of people with dyspnoea , 5 years** 19% with smoking cessation intervention with or without ipratropium 24% with usual care Absolute numbers not reported	P <0.0001	○○○	smoking cessation intervention with or without ipratropium

Quality of life

No data from the following reference on this outcome. [83] [89]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] [90] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean	**Adverse effects (any)** with smoking cessation with or without ipratropium with usual care			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	The RCT reported that 31% (about 1216 people) were still using nicotine gum after 1 year About 25% of these reported at least one adverse effect, but most were minor and transient. The most common adverse effects were: indigestion (5% for men and 4% for women), mouth irritation (6.2% for men and 6.5% for women), mouth ulcers (4% for men and 5% for women), nausea (2% for men and 4% for women), and hiccups (3% for men and 4% for women)			
[91] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Weight gain , 1 year** 2.61 kg for men, 2.63 kg for women with smoking cessation with or without ipratropium 0.61 kg for men, 1.10 kg for women with usual care	Significance not assessed		
[91] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Weight gain , 5 years** 3.9 kg for men, 4.75 kg for women with smoking cessation with or without ipratropium 2.6 kg for men, 2.84 kg for women with usual care	Significance not assessed		

Psychosocial plus pharmacological interventions versus psychosocial intervention alone:

We found one systematic review (search date 2002), [83] which identified two RCTs examining psychosocial plus pharmacological interventions compared with psychosocial intervention alone in people with COPD. [10] [92] One RCT reported only abstinence rates and adverse effects. [92] This study did not provide data about the effects on FEV_1 changes, peak expiratory flow, exacerbations, dyspnoea score, quality of life, or survival.

Mortality

Psychosocial plus pharmacological interventions compared with psychosocial intervention alone Nicotine gum plus a psychosocial smoking cessation and abstinence maintenance programme with ipratropium is no more effective at reducing mortality at 5 years in people with signs of early COPD (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[85] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day Further report of reference [10] The third arm assessed usual care See further information on studies for full description of smoking intervention programme [86]	**All-cause mortality , 5 years** 54/1961 (3%) with smoking cessation intervention plus ipratropium 44/1962 (2%) with smoking cessation intervention alone Absolute numbers not reported 3923 people in this analysis	P = 0.304 (smoking cessation intervention plus ipratropium *v* smoking cessation intervention alone)	⟷	Not significant

Lung function and exercise capacity

Psychosocial plus pharmacological interventions compared with psychosocial intervention alone Nicotine gum plus a psychosocial smoking cessation and abstinence maintenance programme with ipratropium is more effective at reducing the decline in FEV_1 at 1 to 5 years in people with signs of early COPD (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[10] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] The third arm assessed the effects of usual care See further information on studies for full description of smoking intervention programme [86]	**Change in FEV_1 , 1 year** +38.8 mL with smoking cessation intervention plus ipratropium +11.2 mL with smoking cessation alone	P <0.005 (smoking cessation intervention plus ipratropium *v* smoking cessation intervention alone)	○○○	smoking cessation intervention plus ipratropium
[10] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] The third arm assessed the effects of usual care	**Change in FEV_1 , 5 years** –184 mL with smoking cessation intervention plus ipratropium –208 mL with smoking cessation alone	P = 0.002 or less (smoking cessation intervention plus ipratropium *v* smoking cessation intervention alone) Results from completer analysis (about 90% of people)	○○○	smoking cessation intervention plus ipratropium

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	See further information on studies for full description of smoking intervention programme [86]				

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [10]

Quality of life

No data from the following reference on this outcome. [10]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] [90] RCT **3-armed trial**	5887 smokers, aged 35 to 60 years, with spirometric signs of early COPD; mean pre-bronchodilator FEV_1 2640 mL, mean of 30 cigarettes smoked/day In review [83] See further information on studies for full description of smoking intervention programme [86]	**Adverse effects (any)** with smoking cessation intervention plus ipratropium with smoking cessation alone The RCT reported that 31% (about 1216 people) were still using nicotine gum after 1 year About 25% of these reported at least 1 adverse effect, but most were minor and transient. The most common adverse effects were: indigestion (5% for men and 4% for women), mouth irritation (6.2% for men and 6.5% for women), mouth ulcers (4% for men and 5% for women), nausea (2% for men and 4% for women), and hiccups (3% for men and 4% for women)			
[92] RCT	404 people with mild or moderate COPD, smoking an average of 28 cigarettes a day, mean age 54 years In review [83]	**Proportion of people discontinuing treatment because of adverse effects , 6 months** 7% with bupropion (slow-release 150 mg twice daily) plus counselling 6% with placebo plus counselling Absolute numbers not reported	Significance not assessed		
[92] RCT	404 people with mild or moderate COPD, smoking an average of 28 cigarettes a day, mean age 54 years In review [83]	**Proportion of people with a serious adverse event , 6 months** 0.5% with bupropion (slow-release 150 mg twice daily) plus counselling	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2.5% with placebo plus counselling Absolute numbers not reported			

Further information on studies

[86] The smoking cessation intervention consisted of an intensive 12-session smoking cessation programme combining behaviour modification and use of nicotine gum (nicotine polacrilex 2 mg) with a continuing 5-year maintenance programme that included monitoring of weight gain and nutritional counselling.

[95] Smoking cessation intervention significantly reduced self-reported lower respiratory illnesses resulting in physician visits compared with usual care at 5 years (results presented graphically; P = 0.0008).

[92] The RCT found that bupropion plus counselling significantly increased continuous abstinence rates from weeks 4 to 26 compared with counselling alone (16% with bupropion plus counselling *v* 9% with counselling alone; P = 0.05).

Comment: One RCT identified by the review [83] found that the smoking cessation intervention (with or without ipratropium) increased the proportion of sustained quitters at 5 years, with a similar proportion remaining abstinent at 11 years, compared with usual care (22% at 5 years and 21.9% at 11 years with smoking cessation intervention *v* 5% at 5 years and 6% at 11 years with usual care; P value not reported). [96] [10]

QUESTION What are the effects of non-drug interventions in people with stable COPD?

OPTION PULMONARY REHABILITATION

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Multi-modality pulmonary rehabilitation can improve exercise capacity, dyspnoea, and health-related quality of life in people with stable COPD.

Benefits and harms

Pulmonary rehabilitation versus usual care:

We found two systematic reviews (search date 2004, 31 RCTs; [97] and search date 2000, 20 RCTs, 12 of which were also included in the first systematic review [98]), which assessed effects of pulmonary rehabilitation on lung function and rates of COPD exacerbations. The reviews included RCTs of both hospital- and home-based programmes. We found 4 subsequent RCTs assessing similar outcomes for hospital-based rehabilitation. [99] [100] [101] [102] Another systematic review (search date 2006, 6 RCTs, 5 of which were included in the first systematic review [97]) specifically assessed the effects of pulmonary rehabilitation on anxiety and depression. [103] In addition, we found two subsequent RCTs [104] [105] assessing exclusively home-based pulmonary rehabilitation.

Lung function and exercise capacity

Compared with usual care Multi-modality pulmonary rehabilitation seems more effective at improving exercise capacity (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exercise capacity					
[97] Systematic review	511 people 13 RCTs in this analysis	**Difference in incremental cycle ergometer test** with pulmonary rehabilitation	WMD 8.43 watts 95% CI 3.45 watts to 13.41 watts	○○○	pulmonary rehabilitation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with usual care Absolute results not reported The review included RCTs of both hospital- and home-based rehabilitation	There is no generally accepted minimal clinically important difference for the cycle ergometer test		
[97] Systematic review	669 people 16 RCTs in this analysis	**Difference in 6-minute walk distance (6MWD)** with pulmonary rehabilitation with usual care Absolute results not reported The review included RCTs of both hospital- and home-based rehabilitation	WMD 48.46 m 95% CI 31.64 m to 68.28 m The lower limit CI for functional exercise capacity is above the minimal clinically significant difference of between 30 m and 42 m for the 6-minute walk test	○○○	pulmonary rehabilitation
[98] Systematic review	979 people with symptomatic COPD or impaired exercise capacity 20 RCTs in this analysis	**Difference in walking test** with pulmonary rehabilitation with usual care Absolute results not reported The review included RCTs of both hospital- and home-based rehabilitation	Standard effect size 0.71 95% CI 0.43 to 0.99	○○○	pulmonary rehabilitation
[99] RCT	40 men with COPD	**Change in 6MWD from baseline , 16 weeks** from 347 m to 410 m with pulmonary rehabilitation from 330 m to 308 m with control The RCT assessed hospital-based rehabilitation	P <0.01 Randomisation was not concealed	○○○	pulmonary rehabilitation
[105] RCT	78 people with COPD Prospective study	**Change in 6MWD from baseline , 3 months** from 312 m to 328 m (+16 m) with pulmonary rehabilitation from 305 m to 298 m (–7 m) with standard care Pulmonary rehabilitation was performed by patients at home under supervision by a relative. Participants were not visited by a health practitioner but completed a weekly telephone questionnaire	P <0.001 for comparisons from baseline (significant increase with pulmonary rehabilitation; significant decrease with standard care) Increase with pulmonary rehabilitation was below the accepted minimal clinically important difference	○○○	pulmonary rehabilitation
[102] RCT	54 people with mild to moderate COPD (FEV_1 30–80% predicted)	**Change in 6MWD from baseline , 8 weeks** from 262 m to 382 m (+120 m) with pulmonary rehabilitation from 227 m to 242 m (+15 m) with control The RCT assessed a hospital-based outpatient programme of pulmonary rehabilitation See comment below for details of results at longer follow-up	P <0.05 for comparison between groups	○○○	pulmonary rehabilitation
[101] RCT	30 people with COPD	**Change in 6MWD from baseline , 12 weeks** +40.6 with pulmonary rehabilitation	P <0.05 Improvement with pulmonary rehabilitation was below the threshold of clinical importance	○○○	pulmonary rehabilitation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		+16.5 with control The RCT assessed hospital-based pulmonary rehabilitation			
[104] RCT	39 people with COPD	**Mean difference in 6MWD , 8 weeks** from 89 m to 142 m (+53 m) with home-based pulmonary rehabilitation from 84 m to 69 m (–15 m) with control Randomisation was 2:1	P <0.001 Assessors were not blinded	○○○	home-based pulmonary rehabilitation

No data from the following reference on this outcome. [100] [103]

COPD exacerbation and worsening of symptoms

Multi-modality pulmonary rehabilitation compared with usual care Multi-modality pulmonary rehabilitation seems more effective at improving shortness of breath and dyspnoea (as assessed using the Chronic Respiratory Disease Questionnaire) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[97] Systematic review	610 people 11 RCTs in this analysis	**Difference in dyspnoea component of Chronic Respiratory Disease Questionnaire (CRQ)** with pulmonary rehabilitation with usual care Absolute results not reported The review included RCTs of both hospital- and home-based rehabilitation	WMD 1.06 95% CI 0.85 to 1.26 The effect was larger than the minimally clinically important difference of 0.5 units	○○○	pulmonary rehabilitation
[98] Systematic review	723 people 12 RCTs in this analysis	**Difference in shortness of breath (measured by CRQ)** with pulmonary rehabilitation with usual care Absolute results not reported The review included RCTs of both hospital- and home-based rehabilitation	Standard effect size 0.62 95% CI 0.26 to 0.91	○○○	pulmonary rehabilitation
[99] RCT	40 men with COPD	**Change in dyspnoea component of CRQ from baseline , 16 weeks** from 2.9 to 3.7 with pulmonary rehabilitation from 3.6 to 3.4 with control The RCT assessed hospital-based rehabilitation	P <0.01 Randomisation was not concealed	○○○	pulmonary rehabilitation
[104] RCT	39 people with COPD	**Mean difference in dyspnoea component of CRQ , 8 weeks** from 11.8 to 19.6 (+7.8) with home-based pulmonary rehabilitation from 12.4 to 13.5 (+1.1) with control	P = 0.003	○○○	home-based pulmonary rehabilitation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT assessed home-based rehabilitation Randomisation was 2:1 Assessors were not blinded			

No data from the following reference on this outcome. [100] [101] [102] [103] [105]

Quality of life

Compared with usual care Multi-modality pulmonary rehabilitation seems more effective at improving the fatigue, emotional function, and mastery components of the Chronic Respiratory Disease Questionnaire, and at improving the symptoms, activity, and impact domains of the St George's Respiratory Questionnaire, and at modestly improving anxiety and depression (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[97] Systematic review	618 people 11 RCTs in this analysis	**Difference in fatigue component of Chronic Respiratory Disease Questionnaire (CRQ)** with pulmonary rehabilitation with usual care Absolute results not reported The review included RCTs of both home- and hospital-based rehabilitation	WMD 0.92 95% CI 0.71 to 1.13 The effect was larger than the minimally clinically important difference of 0.5 units	○○○	pulmonary rehabilitation
[104] RCT	39 people with COPD	**Mean difference in fatigue component of CRQ , 8 weeks** from 9.8 to 17.4 (+7.6) with home-based pulmonary rehabilitation from 11.6 to 13.2 (+1.6) with control The RCT assessed home-based rehabilitation Randomisation was 2:1 Assessors were not blinded	P <0.004	○○○	home-based pulmonary rehabilitation
[97] Systematic review	618 people 11 RCTs in this analysis	**Difference in emotional function component of CRQ** with pulmonary rehabilitation with usual care Absolute results not reported The review included RCTs of both home- and hospital-based rehabilitation	WMD 0.76 95% CI 0.52 to 1.00 The effect was larger than the minimally clinically important difference of 0.5 units	○○○	pulmonary rehabilitation
[104] RCT	39 people with COPD	**Mean difference in emotional function component of CRQ , 8 weeks** from 22.1 to 33.5 (+11.4) with home-based pulmonary rehabilitation from 27.0 to 29.7 (+2.7) with control The RCT assessed home-based rehabilitation	P <0.008	○○○	home-based pulmonary rehabilitation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Randomisation was 2:1 Assessors were not blinded			
[97] Systematic review	618 people 11 RCTs in this analysis	**Difference in mastery component of CRQ** with pulmonary rehabilitation with usual care Absolute results not reported The review included RCTs of both home- and hospital-based rehabilitation	WMD 0.97 95% CI 0.74 to 1.20 The effect was larger than the minimally clinically important difference of 0.5 units	○○○	pulmonary rehabilitation
[102] RCT	54 people with mild to moderate COPD (FEV_1 30–80% predicted)	**Difference in symptoms domain of St George's Respiratory Questionnaire (SGRQ) from baseline , 8 weeks** from 60 to 38 (–22) with pulmonary rehabilitation from 60 to 46 (–14) with control See comment below for details of results at longer follow-up The RCT assessed hospital-based rehabilitation	P <0.05	○○○	pulmonary rehabilitation
[102] RCT	54 people with mild to moderate COPD (FEV_1 30–80% predicted)	**Difference in activity domain of SGRQ from baseline , 8 weeks** from 67 to 43 (–24) with pulmonary rehabilitation from 70 to 67 (–3) with control See comment below for details of results at longer follow-up The RCT assessed hospital-based rehabilitation	P <0.05	○○○	pulmonary rehabilitation
[102] RCT	54 people with mild to moderate COPD (FEV_1 30–80% predicted)	**Difference in impact domain of SGRQ from baseline , 8 weeks** from 36 to 17 (–19) with pulmonary rehabilitation from 33 to 33 (no change) with with control See comment below for details of results at longer follow-up The RCT assessed hospital-based rehabilitation	P <0.05	○○○	pulmonary rehabilitation
[100] RCT	24 people with severe COPD	**Difference in symptoms domain of SGRQ from baseline , 8 weeks** from 51 to 40 (–11) with pulmonary rehabilitation from 50 to 49 (–1) with control The RCT assessed hospital-based rehabilitation	P <0.05	○○○	pulmonary rehabilitation
[100] RCT	24 people with severe COPD	**Difference in activity domain of SGRQ from baseline , 8 weeks** from 75 to 63 (–12) with pulmonary rehabilitation from 75 to 79 (+4) with control	P <0.05	○○○	pulmonary rehabilitation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT assessed hospital-based rehabilitation			
[100] RCT	24 people with severe COPD	**Difference in impact domain of SGRQ from baseline , 8 weeks** from 47 to 37 (–10) with pulmonary rehabilitation from 49 to 45 (–4) with control The RCT assessed hospital-based rehabilitation	P >0.05	⟷	Not significant
[101] RCT	30 people with COPD	**Difference in symptoms domain of SGRQ from baseline , 12 weeks** +10.6 with pulmonary rehabilitation –0.5 with control The RCT assessed hospital-based rehabilitation	Significance not assessed		
[101] RCT	30 people with COPD	**Difference in activity domain of SGRQ from baseline , 12 weeks** +2.5 with pulmonary rehabilitation +2.7 with control The RCT assessed hospital-based rehabilitation	Significance not assessed		
[101] RCT	30 people with COPD	**Difference in impact domain of SGRQ from baseline , 12 weeks** +9.7 with pulmonary rehabilitation +3.4 with control The RCT assessed hospital-based rehabilitation	Significance not assessed		
[103] Systematic review	269 people with COPD 3 RCTs in this analysis	**Difference in health-related quality of life (HRQL) anxiety score , 12 months** with pulmonary rehabilitation with standard care Absolute numbers not reported	SMD –0.33 95% CI –0.57 to –0.09 P = 0.008	○○○	pulmonary rehabilitation
[103] Systematic review	269 people with COPD 3 RCTs in this analysis	**Difference in depression score , 12 months** with pulmonary rehabilitation with standard care Absolute numbers not reported The review included RCTs of both home- and hospital-based rehabilitation	SMD –0.58 95% CI –0.93 to –0.23 P = 0.001	○○○	pulmonary rehabilitation
[100] RCT	24 people with severe COPD	**Change in Beck Depression Inventory , 8 weeks** from 14 to 6 (–8) with pulmonary rehabilitation from 18 to 16 (–2) with control The RCT assessed hospital-based rehabilitation	P <0.01	○○○	pulmonary rehabilitation
[100]	24 people with severe COPD	**Change in State Trait Anxiety Inventory , 8 weeks**	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
RCT		from 9 to 8 (–1) with pulmonary rehabilitation from 19 to 21 (+2) with control The RCT assessed hospital-based rehabilitation			

No data from the following reference on this outcome. [98] [99] [105]

Mortality

No data from the following reference on this outcome. [97] [98] [99] [100] [101] [102] [103] [104] [105]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[97] Systematic review	31 RCTs in this analysis	**Adverse effects** with pulmonary rehabilitation with usual care Absolute results not reported The review found no adverse effects with pulmonary rehabilitation The review included RCTs of both home- and hospital-based rehabilitation			
[98] Systematic review	979 people with COPD 20 RCTs in this analysis	**Adverse effects** with pulmonary rehabilitation with usual care Absolute results not reported The review found no adverse effects with pulmonary rehabilitation The review included RCTs of both home- and hospital-based rehabilitation			

No data from the following reference on this outcome. [99] [100] [101] [102] [103] [104] [105]

Further information on studies

Comment: There are indications that the effects of pulmonary rehabilitation without reinforcement do not last longer than 1 year. For example, we have reported results for one RCT [102] for the 8-week treatment period. However, the RCT also reported results at 12 weeks — 4 weeks after the end of treatment. The RCT reported that, although improvements from baseline in 6-minute walk distance and in St George's Respiratory Questionnaire scores were still significant at 12 weeks in favour of pulmonary rehabilitation, these parameters began to deteriorate in the period after the end of treatment.

OPTION INSPIRATORY MUSCLE TRAINING (ALONE)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Inspiratory muscle training may improve lung function and exercise capacity in people with COPD.

Benefits and harms

Inspiratory muscle training (IMT) versus control or no IMT:

We found two systematic reviews (search date 2000, 15 RCTs, number of people included not reported; [106] and search date 2003, 19 RCTs [107]).

Lung function and exercise capacity

Inspiratory muscle training (IMT) compared with control/no IMT IMT (with or without general exercise rehabilitation) may be more effective at improving inspiratory muscle strength, endurance, and exercise-related dyspnoea at rest (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[106] Systematic review	383 people 15 RCTs in this analysis	**Inspiratory muscle strength** with inspiratory muscle training (IMT) (with or without general exercise rehabilitation) with control Absolute results not reported	WMD 0.56 cm H_2O 95% CI 0.35 cm H_2O to 0.77 cm H_2O	○○○	IMT
[106] Systematic review	Number of people not reported 7 RCTs in this analysis	**Inspiratory muscle endurance** with IMT (with or without general exercise rehabilitation) with control Absolute results not reported	WMD 0.41 seconds 95% CI 0.14 seconds to 0.68 seconds	○○○	IMT
[106] Systematic review	Number of people not reported 4 RCTs in this analysis	**Inspiratory muscle endurance (maximal voluntary ventilation)** with IMT (with or without general exercise rehabilitation) with control Absolute results not reported	WMD +0.21 L/minute 95% CI –0.29 L/minute to +0.70 L/minute	⟷	Not significant
[107] Systematic review	27 people 2 RCTs in this analysis	**Inspiratory muscle strength** with IMT with no IMT Absolute numbers not reported Results should be interpreted with caution as the review meta-analysed data from only 2 small RCTs	WMD +9.67 cm H_2O 95% CI –4.50 cm H_2O to +23.85 cm H_2O P = 0.18	⟷	Not significant
Exercise capacity					
[106] Systematic review	Number of people not reported 5 RCTs in this analysis	**Laboratory exercise capacity (VO_2 max)** with IMT (with or without general exercise rehabilitation)	WMD +0.04 L/minute 95% CI –0.36 L/minute to +0.29 L/minute	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with control Absolute results not reported			
[106] Systematic review	Number of people not reported 5 RCTs in this analysis	**Laboratory exercise capacity (VE max)** with IMT (with or without general exercise rehabilitation) with control Absolute results not reported	WMD +0.03 L/minute 95% CI –0.03 L/minute to +0.35 L/minute	⟷	Not significant
[106] Systematic review	Number of people not reported 8 RCTs in this analysis	**Functional exercise capacity (6- or 12-minute walking distance)** with IMT (with or without general exercise rehabilitation) with control Absolute results not reported	WMD +0.22 m 95% CI –0.05 m to +0.48 m	⟷	Not significant
[106] Systematic review	Number of people not reported 5 RCTs in this analysis	**Borg exercise-related dyspnoea** with IMT (with or without general exercise rehabilitation) with control Absolute results not reported	WMD –0.55 95% CI –0.90 to +0.19	⟷	Not significant

COPD exacerbation and worsening of symptoms

Inspiratory muscle training (IMT) compared with control/no IMT IMT (with or without general exercise rehabilitation) may be more effective at improving non-exercise-related dyspnoea at rest (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[106] Systematic review	Number of people not reported 2 RCTs in this analysis	**Dyspnoea (as measured by the Transitional Dyspnoea Index)** with IMT (with or without general exercise rehabilitation) with control Absolute results not reported	WMD 2.3 95% CI 1.44 to 3.15	○○○	IMT

No data from the following reference on this outcome. [107]

Mortality

No data from the following reference on this outcome. [106] [107]

Quality of life

No data from the following reference on this outcome. [106] [107]

Inspiratory muscle training (IMT) plus general exercise reconditioning versus general exercise reconditioning alone:

We found one systematic review (search date 2000, 15 RCTs, number of people included not reported). [106]

Lung function and exercise capacity

Inspiratory muscle training (IMT) plus general exercise reconditioning compared with general exercise reconditioning alone IMT plus general exercise reconditioning may be more effective at improving inspiratory muscle strength and inspiratory muscle endurance, but may have no additional benefits on exercise capacity in people with inspiratory muscle weakness (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[106] Systematic review	Number of people not reported 6 RCTs in this analysis	**Inspiratory muscle strength** with inspiratory muscle training (IMT) plus general exercise reconditioning with general exercise reconditioning alone Absolute results not reported	WMD 0.47 cm H_2O 95% CI 0.15 cm H_2O to 0.79 cm H_2O	○○○	IMT plus general exercise reconditioning
[106] Systematic review	Number of people not reported; subgroup analysis of people with inspiratory muscle weakness at baseline 3 RCTs in this analysis	**Inspiratory muscle strength** with IMT plus general exercise reconditioning with general exercise reconditioning alone Absolute results not reported	WMD +16 cm H_2O (CI not reported) P <0.001	○○○	IMT plus general exercise reconditioning
[106] Systematic review	Number of people not reported; subgroup analysis of people without inspiratory muscle weakness at baseline 3 RCTs in this analysis	**Inspiratory muscle strength** with IMT plus general exercise reconditioning with general exercise reconditioning alone Absolute results not reported	WMD –3 cm H_2O (CI not reported) P = 0.54	⟷	Not significant
[106] Systematic review	Number of people not reported 3 RCTs in this analysis	**Inspiratory muscle endurance** with IMT plus general exercise reconditioning with general exercise reconditioning alone Absolute results not reported	WMD 0.55 seconds 95% CI 0.14 seconds to 0.97 seconds	○○○	IMT plus general exercise reconditioning
Exercise capacity					
[106] Systematic review	Number of people not reported 4 RCTs in this analysis	**Functional exercise capacity (6- or 12-minute walk test)** with IMT plus general exercise reconditioning with general exercise reconditioning alone Absolute results not reported	WMD +0.20 m 95% CI –0.21 m to +0.61 m	⟷	Not significant

Mortality

No data from the following reference on this outcome. [106]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [106]

Quality of life

No data from the following reference on this outcome. [106]

Adverse effects

No data from the following reference on this outcome. [106]

Inspiratory muscle training (IMT) versus sham IMT:

We found two systematic reviews (search dates 2003, 19 RCTs, number of people not reported; [107] and 2007, 17 RCTs, 502 people [108]). The second review is largely an update of the first, but we report both here, as the updated review [108] does not report data for all the outcomes reported in the first review. [107]

Lung function and exercise capacity

Inspiratory muscle training (IMT) compared with sham IMT IMT may be more effective at improving inspiratory muscle strength, endurance, Borg dyspnoea rating, and exercise walking distance (6-minute walking test), but may be no more effective at improving exercise capacity, VO_2, and forced vital capacity (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[108] Systematic review	330 people with COPD 13 RCTs in this analysis	**Inspiratory muscle strength , 5 weeks to 6 months** with inspiratory muscle training (IMT) with sham IMT Absolute results not reported	WMD 11.58 cm H_2O 95% CI 8.75 cm H_2O to 14.42 cm H_2O P <0.001	○○○	IMT
[108] Systematic review	143 people 4 RCTs in this analysis	**Inspiratory threshold loading , 5 to 24 weeks** with IMT with sham IMT Absolute results not reported	WMD 1.36 kPa 95% CI 0.79 kPa to 1.94 kPa P <0.001	○○○	IMT
[108] Systematic review	109 people 4 RCTs in this analysis	**Borg scale for respiratory effort , 5 to 24 weeks** with IMT with sham IMT Absolute results not reported	WMD –1.76 95% CI –2.35 to –1.16 P <0.001	○○○	IMT
[108] Systematic review	147 people 4 RCTs in this analysis	**Inspiratory muscle endurance , 5 to 8 weeks** with IMT with sham IMT	WMD +4.43 minutes 95% CI +0.66 minutes to +8.21 minutes P = 0.02	○○○	IMT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[107] Systematic review	56 people 3 RCTs in this analysis	**Forced vital capacity** with IMT with sham IMT Absolute results not reported	WMD +0.22 L 95% CI –0.11 L to +0.54 L P = 0.19	⟷	Not significant
[107] Systematic review	70 people 4 RCTs in this analysis	**FEV_1** with IMT with sham IMT Absolute results not reported	WMD +0.05 L 95% CI –0.02 L to +0.12 L P = 0.15	⟷	Not significant
Exercise capacity					
[108] Systematic review	87 people 5 RCTs in this analysis	**Exercise capacity , 5 to 24 weeks** with IMT with sham IMT Absolute results not reported	WMD –0.05 L/minute 95% CI –0.17 L/minute to +0.07 L/minute P = 0.38	⟷	Not significant
[108] Systematic review	103 people 2 RCTs in this analysis	**6-minute walk distance (6MWD) , 5 to 10 weeks** with IMT with sham IMT Absolute results not reported	WMD 32.13 m 95% CI 11.55 m to 52.72 m P = 0.002	○○○	IMT

COPD exacerbation and worsening of symptoms

Inspiratory muscle training (IMT) compared with sham IMT IMT may be more effective at improving dyspnoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[108] Systematic review	96 people 5 RCTs in this analysis	**Transitional dyspnoea index , 8 weeks to 12 months** with IMT with sham IMT Absolute results not reported	WMD 2.55 95% CI 0.92 to 4.19 P = 0.002	○○○	IMT

Quality of life

Compared with sham inspiratory muscle training (IMT) IMT may be marginally more effective at improving quality of life as assessed by the Chronic Respiratory Disease Questionnaire, although the extent of the improvement may not be clinically meaningful (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Health-related quality of life					
[108] Systematic review	69 people 2 RCTs in this analysis	**Chronic Respiratory Disease Questionnaire (CRQ) total score , 5 to 8 weeks** with inspiratory muscle training (IMT) with sham IMT Absolute results not reported	WMD 0.33 95% CI 0.19 to 0.47 P <0.001	○○○	IMT

Mortality

No data from the following reference on this outcome. [108]

Adverse effects

No data from the following reference on this outcome. [107] [108]

Further information on studies

Comment: None.

OPTION PERIPHERAL MUSCLE STRENGTH TRAINING (ALONE)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Although peripheral muscle strength training improves upper-body and leg strength, it may be no more effective at improving walking endurance; however, it may improve exercise capacity in people with COPD.

Benefits and harms

Peripheral muscle training versus no treatment or other exercise training:

We found one systematic review (search date 2008, 18 RCTs, 534 people). [109] The review included RCTs comparing resistive training versus control, resistive training versus aerobic training, and resistive training plus aerobic training versus aerobic training.

Lung function and exercise capacity

Compared with no treatment or other exercise training Peripheral muscle strength training may be no more effective at improving walking endurance at 6 to 12 weeks, although it may be more effective at improving exercise capacity at 8 to 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[109] Systematic review	158 people with COPD 4 RCTs in this analysis	**6-minute walk distance (6MWD) , 6 to 12 weeks** with peripheral muscle training with no treatment Absolute numbers not reported	Effect size +0.30 95% CI –0.02 to +0.61 P = 0.06	⟷	Not significant
[109] Systematic review	103 people with COPD 3 RCTs in this analysis	**6MWD , 12 weeks** with peripheral muscle training with aerobic training Absolute results not reported	Effect size +0.05 95% CI –0.34 to +0.43 P = 0.82	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exercise capacity					
[109] Systematic review	52 people with COPD 2 RCTs in this analysis	**Cycling endurance , 8 to 12 weeks** with peripheral muscle training with no treatment Absolute results not reported	Effect size 0.87 95% CI 0.29 to 1.44 P = 0.004	○○○	peripheral muscle training
[109] Systematic review	63 people with COPD 2 RCTs in this analysis	**Cycling endurance , 8 to 12 weeks** with peripheral muscle training with aerobic training Absolute results not reported	Effect size –0.89 95% CI –1.82 to –0.36 P = 0.0008	○○○	peripheral muscle training

Quality of life

No data from the following reference on this outcome. [109]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [109]

Mortality

No data from the following reference on this outcome. [109]

Adverse effects

No data from the following reference on this outcome. [109]

Further information on studies

Comment: We found two small systematic reviews assessing the effects of upper-extremity muscle-strength training on COPD. [110] [111] Owing to significant methodological heterogeneity, neither review performed a meta-analysis. The reviews both concluded that upper-extremity muscle-strength training improves upper-extremity exercise capacity but has an uncertain, if any, effect on dyspnoea and on health-related quality of life. [110] [111]

OPTION GENERAL PHYSICAL ACTIVITY ENHANCEMENT (ALONE)

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- General physical exercises can improve exercise capacity in people with stable COPD.

Benefits and harms

General physical activity enhancement versus control:

We found one systematic review (search date 1999) investigating general physical activity enhancement (walking, cycling, or swimming, and/or training of most large muscle groups). [112] The review did not present meta-analyses of outcomes and so we report data from individual RCTs. We found one subsequent RCT assessing a pedometer-based exercise enhancement programme. [113]

Lung function and exercise capacity

Compared with control General physical activity enhancement (walking, cycling, or swimming) may be more effective at improving exercise tolerance (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exercise capacity					
[112] Systematic review	48 people Data from 1 RCT	**Walking test** with physical activity with control Absolute results not reported	Difference 5942 joules 95% CI presented graphically	○○○	physical activity
[112] Systematic review	43 people Data from 1 RCT	**Walking test** with physical activity with control Absolute results not reported	Difference 3861 joules 95% CI presented graphically	○○○	physical activity
[112] Systematic review	38 people Data from 1 RCT	**6-minute walking distance test (6MWD)** with physical activity with control Absolute results not reported	Difference 29 m 95% CI presented graphically	⟷	Not significant
[112] Systematic review	23 people Data from 1 RCT	**6MWD** with physical activity with control Absolute results not reported	Difference 5 m 95% CI presented graphically	⟷	Not significant
[113] RCT	39 people with COPD	**Change in 6MWD from baseline , 12 weeks** from 365 m to 387 m (+22 m) with pedometer-based exercise counselling programme from 351 m to 361 m (+10 m) with control	P = 0.09 Improvement in exercise counselling group not clinically significant	⟷	Not significant
[112] Systematic review	58 people Data from 1 RCT	**Cycle ergometer** with physical activity with control Absolute results not reported	24.7 watts 95% CI presented graphically	○○○	physical activity

COPD exacerbation and worsening of symptoms

Compared with control We don't know whether general physical activity enhancement is more effective at improving dyspnoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Shortness of breath					
[114] RCT	23 people In review [112]	**Mean change in dyspnoea component of Chronic Respiratory Disease Questionnaire (CRQ) score (range 5–35)** 6 with physical activity 0 with control	Significance not reported for COPD subgroup		
[115] RCT	38 people In review [112]	**Mean change in Borg dyspnoea scale after walking test** 0.4 with physical activity 0.9 with control	Difference –0.5 95% CI –1.5 to +0.6	⟷	Not significant

No data from the following reference on this outcome. [113]

Quality of life

Compared with control We don't know whether general physical activity enhancement is more effective at improving quality-of-life scores (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[114] RCT	23 people In review [112]	**Mean change in fatigue component of Chronic Respiratory Disease Questionnaire (CRQ) score (range 4–28)** 5 with physical activity 0 with control	Significance not reported for COPD subgroup		
[114] RCT	23 people In review [112]	**Mean change in emotion component of CRQ score (range 7–49)** 5 with physical activity 2 with control	Significance not reported for COPD subgroup		
[114] RCT	23 people In review [112]	**Mean change in mastery component of CRQ score (range 4–28)** +4 with physical activity –1 with control	Significance not reported for COPD subgroup		
[115] RCT	38 people In review [112]	**Mean change in the St George's Respiratory Questionnaire (SGRQ) total score** –2.1 with physical activity –2.1 with control	Difference +0.1 95% CI –9.9 to +10.0	⟷	Not significant
[113] RCT	39 people with COPD	**Change in SGRQ total from baseline , 12 weeks** from 37.7 to 34.2 (–3.5) with pedometer-based exercise counselling programme from 35.2 to 38.3 (+3.1) with control	P = 0.05	⟷	Not significant

Mortality

No data from the following reference on this outcome. [112] [113]

Adverse effects

No data from the following reference on this outcome. [112] [113]

Further information on studies

Comment: None.

OPTION NUTRITIONAL SUPPLEMENTATION

- For GRADE evaluation of interventions for COPD, see table, p 95 .
- Nutritional supplementation has not been shown to be beneficial at improving lung function and exercise capacity of people with COPD.

Benefits and harms

Nutritional supplementation versus placebo or usual diet:

We found two systematic reviews. [116] [117] The second systematic review identified 21 RCTs, which were classified according to the type (different composition of carbohydrates/fat), duration of supplementation (1 meal, <2 weeks, >2 weeks), and presence of anabolic substances. [117] Overall, 11 RCTs examined supplementation for at least 2 weeks, without the use of anabolic substances, in a total of 327 people. Nine of the RCTs were common to the first systematic review. [116]

Lung function and exercise capacity

Compared with placebo/usual diet Nutritional supplementations may be no more effective at improving lung function or exercise capacity in people with stable COPD (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[116] Systematic review	156 people 6 RCTs in this analysis	**FEV_1** with nutritional supplementation for 2 weeks with placebo or usual diet Absolute results not reported	SMD –0.12 95% CI –0.44 to +0.20	⟷	Not significant
[116] Systematic review	152 people 6 RCTs in this analysis	**Maximal inspiratory pressure** with nutritional supplementation for 2 weeks with placebo or usual diet Absolute results not reported	SMD +0.22 95% CI –0.10 to +0.55	⟷	Not significant
[116] Systematic review	152 people 6 RCTs in this analysis	**Maximal expiratory pressure** with nutritional supplementation for 2 weeks with placebo or usual diet	SMD +0.28 95% CI –0.05 to +0.60	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
Exercise capacity					
[116] Systematic review	77 people 3 RCTs in this analysis	**6-minute walk distance** with nutritional supplementation for 2 weeks with placebo or usual diet Absolute results not reported	SMD –0.01 95% CI –0.46 to +0.44	⟷	Not significant

Mortality

No data from the following reference on this outcome. [116] [117]

COPD exacerbation and worsening of symptoms

No data from the following reference on this outcome. [116] [117]

Quality of life

No data from the following reference on this outcome. [116] [117]

Adverse effects

No data from the following reference on this outcome. [116] [117]

Further information on studies

[116] The review found similar weight gain with nutritional supplementation and placebo or usual diet for at least 2 weeks (search date 2006, 12 RCTs, 419 people; SMD +0.16, 95% CI –0.09 to +0.42; absolute numbers not reported). It also found similar changes in arm muscle circumference, and triceps skinfold thickness with nutritional supplementation and placebo or usual diet for at least 2 weeks (arm muscle circumference: 8 RCTs, 214 people; SMD +0.07, 95% CI –0.27 to +0.41; triceps skinfold thickness: 6 RCTs, 124 people; SMD +0.35, 95% CI 0 to +0.71).

[117] The review found that nutritional supplementation increased mean weight gain compared with control (mean weight gain: +1.87 kg with nutritional supplementation *v* –0.03 kg with control; significance not reported). Again, no consistent effects on anthropometric measures or pulmonary function were demonstrated (data not reported).

Comment: The two systematic reviews are difficult to interpret because of heterogeneity among the RCTs. The interventions were not standardised, and varied in terms of energy, protein, fat, and carbohydrate content, and in terms of route of administration and duration and frequency of supplementation. The RCTs did not frequently control for reaching a positive energy balance, but the studies that

accomplished an increased (net) energy input also demonstrated functional improvements. [118] Other variations between the studies included: outcome variables, severity of COPD and comorbidities, setting of interventions (at home, pulmonary rehabilitation, admitted to hospital), addition of exercise and anabolic steroids, and methodological quality.

GLOSSARY

Forced expiratory volume in 1 second (FEV_1) The volume breathed out in the first second of forceful blowing into a spirometer, measured in litres.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Peak expiratory flow The maximum flow of gas that is expired from the lungs when blowing into a peak flow meter or a spirometer; the units are expressed as litres per minute.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

$Alpha_1$ antitrypsin New evidence added. [81] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to judge this intervention.

Antibiotics (prophylactic) New evidence added. [77] Categorisation unchanged (Unknown effectiveness) as the evidence is contradictory and much comes from trials completed before 1970.

Anticholinergics New evidence added. [21] [22] [23] [24] Categorisation unchanged (Beneficial).

$Beta_2$ agonists (inhaled) New evidence added. [28] [32] [37] [38] [39] [40] [41] Categorisation unchanged (Beneficial).

Corticosteroids (inhaled) New evidence added. [58] [61] [62] Categorisation unchanged (Beneficial).

Corticosteroids plus long-acting $beta_2$ agonists New evidence added. [65] [66] [67] [68] [70] Categorisation unchanged (Beneficial).

General physical activity enhancement (alone) New evidence added. [113] Categorisation unchanged (Likely to be beneficial).

Inspiratory muscle training New evidence added. [108] Categorisation unchanged (Likely to be beneficial).

Mucolytics New evidence added. [74] Categorisation unchanged (Unknown effectiveness) as all the RCTs we found had methodological flaws.

Peripheral muscle strength training (alone) New evidence added. [109] Categorisation unchanged (Likely to be beneficial).

Pulmonary rehabilitation New evidence added. [100] [101] [102] [103] [104] [105] Categorisation unchanged (Beneficial).

Theophylline New evidence added. [50] [51] Categorisation unchanged (Trade-off between benefits and harms).

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GRADE **Evaluation of interventions for COPD.**

Important outcomes		COPD exacerbation and worsening of symptoms, Lung function and exercise capacity, Mortality, Quality of life							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of maintenance drug treatment in stable COPD?									
4 (1651) [16] [17] [18] [19]	Lung function and exercise capacity	Anticholinergics (short-term treatment) versus placebo	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (780) [18]	COPD exacerbation and worsening of symptoms	Anticholinergics (short-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (780) [18]	Quality of life	Anticholinergics (short-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
17 (17,606) [21] [22] [23] [24]	Mortality	Anticholinergics (long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
9 (4769) [22] [24]	Lung function and exercise capacity	Anticholinergics (long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality points deducted for incomplete reporting of results
9 (4835) [22] [24]	COPD exacerbation and worsening of symptoms	Anticholinergics (long-term treatment) versus placebo	4	0	0	0	0	High	
4 (2386) [22] [24]	Quality of life	Anticholinergics (long-term treatment) versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 7 (at least 405) [26] [28]	Lung function and exercise capacity	Short-acting beta$_2$ agonists (short-term treatment) versus placebo	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity among RCTs
5 (379) [26]	COPD exacerbation and worsening of symptoms	Short-acting beta$_2$ agonists (short-term treatment) versus placebo	4	−1	−2	0	0	Very low	Quality point deducted for incomplete reporting of results. Consistency points deducted for heterogeneity among RCTs included in review and different results for different measures of the same outcome
13 (8400) [32]	Mortality	Long-acting beta$_2$ agonists (short-term or long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (1797) [29] [30] [19] [33] [34] [36] [37] [38] [39]	Lung function and exercise capacity	Long-acting beta$_2$ agonists (short-term or long-term treatment) versus placebo	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results for outcomes assessing exercise capacity
20 (8614) [32] [37] [38] [30]	COPD exacerbation and worsening of symptoms	Long-acting beta$_2$ agonists (short-term or long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
12 (8375) [32]	Quality of life	Long-acting beta$_2$ agonists (short-term or long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (2248) [44]	Lung function and exercise capacity	Short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist (short-term treatment) versus short-acting beta$_2$ agonist alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes		COPD exacerbation and worsening of symptoms, Lung function and exercise capacity, Mortality, Quality of life							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
at least 5 (at least 1529) [29] [44]	COPD exacerbation and worsening of symptoms	Short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist (short-term treatment) versus short-acting beta$_2$ agonist alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (1529) [44]	Quality of life	Short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist (short-term treatment) versus short-acting beta$_2$ agonist alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (1186) [29]	COPD exacerbation and worsening of symptoms	Short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist (short-term treatment) versus short-acting anticholinergic alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (94) [46]	Lung function and exercise capacity	Short-acting anticholinergic plus long-acting inhaled beta$_2$ agonist (short-term treatment) versus beta$_2$ agonist alone	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (172) [47]	Lung function and exercise capacity	Short-acting anticholinergic plus long-acting inhaled beta$_2$ agonist (short-term treatment) versus short-acting anticholinergic plus short-acting inhaled beta$_2$ agonist	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
6 (1917) [44]	Lung function and exercise capacity	Short-acting anticholinergic versus short-acting beta$_2$ agonist	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (1529) [44]	COPD exacerbation and worsening of symptoms	Short-acting anticholinergic versus short-acting beta$_2$ agonist	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (1529) [44]	Quality of life	Short-acting anticholinergic versus short-acting beta$_2$ agonist	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 2 (at least 471) [45]	Lung function and exercise capacity	Short-acting anticholinergic versus long-acting beta$_2$ agonist	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (1241) [30]	COPD exacerbation and worsening of symptoms	Short-acting anticholinergic versus long-acting beta$_2$ agonist	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (467) [45]	Quality of life	Short-acting anticholinergic versus long-acting beta$_2$ agonist	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (1460) [48]	Mortality	Long-acting anticholinergic versus long-acting beta$_2$ agonist	4	0	0	0	0	High	
2 (1382) [48]	Lung function and exercise capacity	Long-acting anticholinergic versus long-acting beta$_2$ agonist	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (1460) [48]	COPD exacerbation and worsening of symptoms	Long-acting anticholinergic versus long-acting beta$_2$ agonist	4	0	0	0	0	High	
2 (807) [30]	Quality of life	Long-acting anticholinergic versus long-acting beta$_2$ agonist	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes		COPD exacerbation and worsening of symptoms, Lung function and exercise capacity, Mortality, Quality of life							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
at least 11 (at least 740) [49] [50] [51]	Lung function and exercise capacity	Theophylline (short-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (964) [52] [53]	Lung function and exercise capacity	Theophylline (long-term treatment) versus placebo	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for inclusion of a 3-armed RCT with 1 open-label arm
1 (110) [53]	COPD exacerbation and worsening of symptoms	Theophylline (long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
10 (445) [55]	Lung function and exercise capacity	Oral corticosteroids versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (424) [58]	Lung function and exercise capacity	Inhaled corticosteroids (short-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (15,407) [62] [35]	Mortality	Inhaled corticosteroids (long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for poor methodology in 1 very large RCT (analysis included people who had discontinued study medication)
6 (at least 3747) [58] [63] [64]	Lung function and exercise capacity	Inhaled corticosteroids (long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
13 (9578) [61] [63] [64]	COPD exacerbation and worsening of symptoms	Inhaled corticosteroids (long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (3230) [58] [64]	Quality of life	Inhaled corticosteroids (long-term treatment) versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
9 (7342) [65] [66] [67]	Mortality	Corticosteroid plus long-acting beta$_2$ agonist versus placebo	4	0	0	0	0	High	
10 (4070) [65] [68] [66] [67]	Lung function and exercise capacity	Corticosteroid plus long-acting beta$_2$ agonist versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (5804) [65] [67] [68]	COPD exacerbation and worsening of symptoms	Corticosteroid plus long-acting beta$_2$ agonist versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (5205) [65] [68]	Quality of life	Corticosteroid plus long-acting beta$_2$ agonist versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (6682) [69] [66]	Mortality	Corticosteroid plus long-acting beta$_2$ agonist versus corticosteroid alone	4	0	0	0	0	High	
6 (1831) [69] [68]	Lung function and exercise capacity	Corticosteroid plus long-acting beta$_2$ agonist versus corticosteroid alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (4930) [69] [68]	COPD exacerbation and worsening of symptoms	Corticosteroid plus long-acting beta$_2$ agonist versus corticosteroid alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 5 (at least 3697) [69]	Quality of life	Corticosteroid plus long-acting beta$_2$ agonist versus corticosteroid alone	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
11 (10,013) [70]	Mortality	Corticosteroid plus long-acting beta$_2$ agonist versus beta$_2$ agonist alone	4	–1	0	0	0	Moderate	Quality point deducted for unclear allocation concealment in some RCTs

Important outcomes		COPD exacerbation and worsening of symptoms, Lung function and exercise capacity, Mortality, Quality of life							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
13 (10,695) [70]	Lung function and exercise capacity	Corticosteroid plus long-acting beta$_2$ agonist versus beta$_2$ agonist alone	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and unclear allocation concealment in some RCTs
at least 14 (at least 12,297) [70]	COPD exacerbation and worsening of symptoms	Corticosteroid plus long-acting beta$_2$ agonist versus beta$_2$ agonist alone	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and unclear allocation concealment in some RCTs
10 (9329) [71] [70]	Quality of life	Corticosteroid plus long-acting beta$_2$ agonist versus beta$_2$ agonist alone	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and unclear allocation concealment in some RCTs
at least 7 (at least 5764) [72] [73] [74]	COPD exacerbation and worsening of symptoms	Mucolytics (long-term treatment) versus placebo	4	−1	−2	−1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency points deducted for conflicting results and for heterogeneity among RCTs. Directness point deducted for inclusion of people without COPD
11 (2625) [72] [74]	Quality of life	Mucolytics (long-term treatment) versus placebo	4	−1	−1	−1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity among RCTs. Directness point deducted for inclusion of people without COPD
1 (709) [74]	Lung function and exercise capacity	Mucolytics (long-term treatment) versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting. Directness point deducted for differences in additional medications between groups at baseline
11 (at least 888) [76] [77]	COPD exacerbation and worsening of symptoms	Prophylactic antibiotics versus placebo	4	−1	0	−2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for inclusion of people without COPD and uncertainty about generalisability of results as some included trials were >30 years old
7 (755) [76]	Quality of life	Prophylactic antibiotics versus placebo	4	−1	0	−2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for inclusion of people without COPD and uncertainty about generalisability of results as some included trials were >30 years old
1 (109) [77]	Lung function and exercise capacity	Prophylactic antibiotics versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for possible drug–drug interactions
3 (250) [78]	Mortality	Oxygen versus no oxygen (long-term treatment)	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results in different populations
1 (28) [78]	Lung function and exercise capacity	Oxygen versus no oxygen (long-term treatment)	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (28) [78]	COPD exacerbation and worsening of symptoms	Oxygen versus no oxygen (long-term treatment)	4	−1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes		COPD exacerbation and worsening of symptoms, Lung function and exercise capacity, Mortality, Quality of life							
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (56) [81]	Lung function and exercise capacity	$Alpha_1$ antitrypsin versus placebo (long-term treatment)	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrowness of population (people with diagnosis of emphysema)
What are the effects of smoking cessation interventions in people with stable COPD?									
1 (3926) [85]	Mortality	Psychosocial interventions versus usual care	4	0	0	−1	0	Moderate	Directness point deducted for combined analysis at long-term analysis (analysis at 14 years, includes smoking cessation with ipratropium)
1 (5887) [10]	Lung function and exercise capacity	Psychosocial interventions versus usual care	4	0	0	−1	0	Moderate	Directness point deducted for combined analysis at long-term analysis (analysis at 11 years includes smoking cessation with ipratropium)
1 (5887) [89]	COPD exacerbation and worsening of symptoms	Psychosocial interventions versus usual care	4	0	0	−1	0	Moderate	Directness point deducted for combined analysis (includes smoking cessation with ipratropium)
1 (3925) [85]	Mortality	Psychosocial plus pharmacological interventions versus usual care	4	0	0	−1	0	Moderate	Directness point deducted for combined analysis for long-term results (analysis at 14 years includes smoking cessation without ipratropium)
1 (5887) [10]	Lung function and exercise capacity	Psychosocial plus pharmacological interventions versus usual care	4	0	0	−1	0	Moderate	Directness point deducted for combined analysis at 11 years (includes smoking cessation without ipratropium)
1 (5887) [89]	COPD exacerbation and worsening of symptoms	Psychosocial plus pharmacological interventions versus usual care	4	0	0	−1	0	Moderate	Directness point deducted for combined analysis at 11 years (includes smoking cessation without ipratropium)
1 (3923) [85]	Mortality	Psychosocial plus pharmacological interventions versus psychosocial intervention alone	4	0	0	0	0	High	
1 (5887) [10]	Lung function and exercise capacity	Psychosocial plus pharmacological interventions versus psychosocial intervention alone	4	0	0	0	0	High	
What are the effects of non-drug interventions in people with stable COPD?									
at least 25 (at least 1220) [97] [98] [99] [105] [102] [101] [104]	Lung function and exercise capacity	Pulmonary rehabilitation versus usual care	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 14 (at least 802) [97] [98] [99] [104]	COPD exacerbation and worsening of symptoms	Pulmonary rehabilitation versus usual care	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 15 (at least 765) [97] [104] [102] [100] [101] [103]	Quality of life	Pulmonary rehabilitation versus usual care	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes		COPD exacerbation and worsening of symptoms, Lung function and exercise capacity, Mortality, Quality of life							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
at least 16 (at least 410) [106] [107]	Lung function and exercise capacity	Inspiratory muscle training (IMT) versus control or no IMT	4	−1	−1	−1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for lack of consistent benefit. Directness point deducted for inclusion of co-intervention (general exercise rehabilitation)
2 (number of people not reported) [106]	COPD exacerbation and worsening of symptoms	Inspiratory muscle training (IMT) versus control or no IMT	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of co-intervention (general exercise rehabilitation)
at least 6 (number of people not reported) [106]	Lung function and exercise capacity	Inspiratory muscle training (IMT) plus general exercise reconditioning versus general exercise reconditioning alone	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for lack of consistent benefit
at least 13 (at least 330) [108] [107]	Lung function and exercise capacity	Inspiratory muscle training (IMT) versus sham IMT	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for lack of consistent benefit
4 (96) [108]	COPD exacerbation and worsening of symptoms	Inspiratory muscle training (IMT) versus sham IMT	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (69) [108]	Quality of life	Inspiratory muscle training (IMT) versus sham IMT	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
at least 7 (at least 261) [109]	Lung function and exercise capacity	Peripheral muscle training versus no treatment or other exercise training	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for lack of consistent benefit
6 (249) [112] [113]	Lung function and exercise capacity	General physical activity enhancement versus control	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for inconsistent effects
2 (61) [114] [115]	COPD exacerbation and worsening of symptoms	General physical activity enhancement versus control	4	−2	−1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
3 (100) [114] [115] [113]	Quality of life	General physical activity enhancement versus control	4	−2	−1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
at least 6 (at least 156) [116]	Lung function and exercise capacity	Nutritional supplementation versus placebo or usual diet	4	−1	−1	−2	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity among RCTs. Directness points deducted for lack of standardisation of interventions and variations among studies

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.