

Chronic obstructive pulmonary disease

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INTERVENTIONS

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Likely to be beneficial

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Beneficial

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Likely to be beneficial

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To be covered in future updates

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Key Messages

Drug treatments

- Inhaled anticholinergics (improved exacerbation rate, symptoms, and FEV₁ compared with placebo)** RCTs found that inhaled anticholinergics improved forced expiratory volume in 1 second, exercise capacity, and symptoms compared with placebo. One large RCT found that adding ipratropium to a smoking cessation programme had no significant impact on decline in forced expiratory volume in 1 second over 5 years compared with the smoking cessation programme alone. RCTs identified by a systematic review found that inhaled tiotropium (a long acting anticholinergic drug) improved exacerbation rates, health related quality of life, and forced expiratory volume in 1 second compared with placebo or ipratropium.

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- **Inhaled anticholinergics plus beta₂ agonists (improved FEV₁ compared with either drug alone)** A systematic review found that combining a short acting beta₂ agonist with an anticholinergic drug (ipratropium) for 12 weeks improved exacerbations compared with the beta₂ agonist alone but not ipratropium alone. One RCT found that combining a long acting beta₂ agonist with an anticholinergic drug did not improve symptoms but modestly improved some measures of lung function compared with the long acting beta₂ agonist alone. One RCT found that, when combined with an anticholinergic drug, a long acting beta₂ agonist improved forced expiratory volume in 1 second and peak expiratory flow more than a short acting beta₂ agonist. We found no RCTs of long term treatment comparing anticholinergics plus beta₂ agonists with placebo.
- **Inhaled beta₂ agonists (improved FEV₁, quality of life and exacerbation rates compared with placebo)** RCTs found that treatment with inhaled beta₂ agonists for 1 week to 12 months improved forced expiratory volume in 1 second compared with placebo. A systematic review and RCTs found that long acting beta₂ agonists for 12–52 weeks improved quality of life and exacerbation rates compared with placebo.
- **Inhaled corticosteroids plus long acting beta₂ agonists (improved exacerbation rate, symptoms, quality of life, FEV₁ compared with placebo)** RCTs found that the combination of an inhaled corticosteroid plus a long acting beta₂ agonist reduced exacerbation rates and improved lung function, symptoms, and health related quality of life compared with placebo in people with moderate to severe disease. In general, the combination was more effective than inhaled corticosteroid alone or long acting beta₂ agonist alone, although this difference was not significant for all outcomes.
- **Inhaled anticholinergics compared with beta₂ agonists (improved FEV₁ compared with beta₂ agonists in long term)** RCTs found inconsistent evidence about the effects of short acting inhaled anticholinergics compared with long acting beta₂ agonists for up to 3 months. Two RCTs identified by a systematic review found that 6 months of a long acting inhaled anticholinergic improved forced expiratory volume in 1 second compared with a long acting inhaled beta₂ agonist. The RCTs found mixed results for health related quality of life and one of the RCTs found no significant difference between a long acting inhaled anticholinergic and a long acting inhaled beta₂ agonist in quality of life or exacerbation rates at 6 months.
- **Long term domiciliary oxygen (beneficial in people with severe hypoxaemia)** One RCT in people with severe daytime hypoxaemia found that domiciliary oxygen improved survival compared with no domiciliary oxygen. A second RCT in people with severe hypoxaemia found that continuous oxygen reduced mortality compared with nocturnal oxygen. Three RCTs in people with milder hypoxaemia or with nocturnal hypoxaemia only, found no significant difference in mortality between long term domiciliary oxygen and no oxygen.
- **Inhaled corticosteroids (improved exacerbation rates, but may have long term harms)** RCTs found no significant difference between inhaled corticosteroids and placebo in lung function (forced expiratory volume in 1 second) over 10 days to 10 weeks. One systematic review and one subsequent RCT found no significant difference in decline in forced expiratory volume in 1 second between inhaled corticosteroids and placebo after 24 months. However, a second systematic review that examined effects of high dose inhaled corticosteroids and four subsequent RCTs found that inhaled corticosteroids slightly reduced the decline in forced expiratory volume in 1 second compared with placebo after 12–24 months. Two systematic reviews and one subsequent RCT found that long term inhaled steroids reduced the frequency of exacerbations compared with placebo. Two subsequent RCTs found no significant difference in exacerbation rates. Long term inhaled steroids may predispose to adverse effects, including skin bruising and oral candidiasis.
- **Theophyllines** One systematic review found that theophyllines slightly improved forced expiratory volume in 1 second compared with placebo after 3 months. One large RCT found that theophyllines improved forced expiratory volume in 1 second compared with placebo after 12 months' treatment. The usefulness of these drugs is limited by adverse effects and the need for frequent monitoring of blood concentrations.
- **Alpha₁ antitrypsin** One RCT in people with alpha₁ antitrypsin deficiency and moderate emphysema found no significant difference between alpha₁ antitrypsin infusion and placebo in the decline in forced expiratory volume in 1 second after 1 year.
- **Mucolytics** Two systematic reviews in chronic bronchitis found limited evidence that mucolytics for 3–24 months reduced the frequency and duration of exacerbations compared with placebo. Two RCTs in chronic obstructive pulmonary disease found no significant difference in decline in forced expiratory volume in 1 second and exacerbations.

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- **Prophylactic antibiotics** One systematic review found limited evidence of a small reduction in exacerbation rates and days with disability with prophylactic antibiotics. These benefits probably do not outweigh the harms of antibiotics, especially the development of antibiotic resistance. All of the identified RCTs were conducted more than 30 years ago, and the results are unlikely to apply to current practice.
- **Oral corticosteroids (evidence of harm but no evidence of long term benefits)** We found no RCTs on long term benefits. One systematic review found that treatment with oral corticosteroids for 2–4 weeks improved forced expiratory volume in 1 second compared with placebo. Long term systemic corticosteroids are associated with serious adverse effects, including osteoporosis and diabetes.

Non-drug interventions

- **Psychosocial plus pharmacological interventions for smoking cessation** One large RCT in people with mild chronic obstructive pulmonary disease found that nicotine gum plus a psychosocial smoking cessation and abstinence maintenance programme (with or without ipratropium) slowed the decline of forced expiratory volume in 1 second, and reduced respiratory symptoms and lower respiratory illnesses, but increased weight gain compared with usual care (without psychosocial intervention). The RCT found no significant difference between treatments in all cause mortality at 5 years, but it found that smoking cessation reduced all cause mortality compared with usual care at 14.5 years.
- **Pulmonary rehabilitation** Two systematic reviews found that multi-modality pulmonary rehabilitation improved quality of life, maximal exercise capacity, and functional exercise capacity.
- **General physical activity** One systematic review found that general physical activity enhancement (walking, cycling, or swimming) improved exercise tolerance compared with control. It found no consistent evidence of a difference in quality of life and dyspnoea.
- **Inspiratory muscle training** One systematic review found that inspiratory muscle training improved inspiratory muscle strength and endurance, and dyspnoea at rest and during exercise compared with control, but it found no significant difference in exercise capacity between groups. The review found that adding inspiratory muscle training to general exercise reconditioning improved inspiratory muscle strength and endurance, but did not have any additional beneficial effects on exercise capacity.
- **Peripheral muscle training** One systematic review found that peripheral muscle training improved upper body and leg strength compared with no treatment or other exercise training. It found that pulmonary function, maximal exercise capacity, walking endurance, cycling endurance, and psychological wellbeing were similar in both groups.
- **Pharmacological interventions alone for smoking cessation** One systematic review found no RCTs of pharmacological interventions alone for smoking cessation in people with chronic obstructive pulmonary disease.
- **Psychosocial interventions alone for smoking cessation** We found no systematic review or RCTs of psychosocial interventions alone for smoking cessation in people with chronic obstructive pulmonary disease.
- **Nutritional supplementation** Two systematic reviews found no consistent evidence that nutritional supplementation improves lung function or exercise capacity in people with stable chronic obstructive pulmonary disease.

DEFINITION

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.¹ Classically, it has been 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 mucus 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 elderly people. In 1998, the World Health Organization 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

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AETIOLOGY/ RISK FACTORS	COPD is largely preventable. The main cause in developed countries is exposure to tobacco smoke. In developed countries, 85–90% 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 hyperresponsiveness, indoor and outdoor air pollution, and allergy. ^{7–9}
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; and to improve activities of daily living, quality of life, and survival. ¹¹
OUTCOMES	Short and long term changes in lung function, including changes in forced expiratory volume in 1 second (FEV ₁); peak expiratory flow [Ⓞ] ; exercise tolerance; frequency, severity, and duration of exacerbations; symptom scores for dyspnoea; quality of life; and survival. Symptom and quality of life scores include the St George’s Respiratory Questionnaire, which is rated on a scale from 0–100 (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 (CRDQ), which is rated from 1–7 (a 0.5 point change is considered clinically important).
METHODS	<i>Clinical Evidence</i> search and appraisal March 2005. This review deals only with treatment of stable COPD and not with treatment of acute exacerbations. We were interested in the maintenance treatment of stable COPD; therefore, we did not include single dose or single day cumulative dose–response trials. In this review, short term treatment is defined as less than 6 months and long term as 6 months or over. There is consensus that 6 months is the absolute minimum duration of treatment required to assess effects on decline in lung function. Where RCTs were found, no systematic search for observational studies was performed. We had articles translated as necessary and included all studies of sufficient quality. If we retrieved multiple systematic reviews which identified the same RCTs, we reported only the most recent review.

QUESTION What are the effects of maintenance drug treatment in stable chronic obstructive pulmonary disorder?

OPTION INHALED ANTICHOLINERGICS

RCTs found that inhaled anticholinergics improved forced expiratory volume in 1 second, exercise capacity, and symptoms compared with placebo. One large RCT found that adding ipratropium to a smoking cessation programme had no significant impact on decline in forced expiratory volume in 1 second over 5 years compared with the smoking cessation programme alone. RCTs identified by a systematic review found that inhaled tiotropium (a long acting anticholinergic drug) improved exacerbation rates, health related quality of life, and forced expiratory volume in 1 second compared with placebo or ipratropium.

Benefits: **Short term short acting anticholinergics:** We found four small^{12–15} and four large^{16–19} RCTs assessing the effects of ipratropium on lung function. We also found one systematic review, which assessed the effects of any anticholinergic drug compared with placebo on exercise capacity.²⁰ All of the RCTs compared three or four interventions: ipratropium (at different doses in one trial), placebo, and a beta₂ agonist. 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. The first two of the large RCTs (276 people¹⁶ and 405 people¹⁷) compared ipratropium (36 µg 4 times daily) versus placebo and salmeterol for 12 weeks. In both RCTs, ipratropium significantly improved baseline forced expiratory volume in 1 second (FEV₁) compared with placebo (results presented graphically). The third large RCT (780 people) compared ipratropium (40 µg 4 times daily) versus placebo and versus formoterol (eforoterol) for 12 weeks.¹⁸ It found that ipratropium significantly improved FEV₁ compared with placebo (improvement in average FEV₁ over 12 hours after medication 137 mL, 95% CI 88 mL to 186 mL). It found no significant difference in morning premedication peak expiratory flow, symptoms, quality of life scores, or need for rescue bronchodilators. The fourth large RCT (183 people with moderate to severe chronic obstructive pulmonary disease,

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mean FEV₁ 40% predicted, mean age 64 years) compared three treatments: ipratropium (80 µg 3 times daily), formoterol (18 µg twice daily), and placebo.¹⁹ It found no significant difference between ipratropium and placebo in shuttle walking distance at 12 weeks (mean increase from baseline: 15.3 m with ipratropium v 6.1 m with placebo; P value not reported, baseline mean distance 325 m). The systematic review (search date 1999) assessed changes in exercise capacity with anticholinergic drugs compared with placebo.²⁰ Meta-analysis was not performed because of heterogeneity in design and outcomes assessed among studies. Sixteen of the 17 RCTs found that any anticholinergic drug improved exercise capacity compared with placebo. **Long term treatment with ipratropium or tiotropium:** We found one systematic review²¹ and one additional RCT.¹⁰ The review found that tiotropium significantly reduced exacerbation rates compared with placebo or ipratropium at 13–52 weeks (search date 2002; placebo: 3 RCTs; 2751 people; RR 0.74, 95% CI 0.62 to 0.89; ipratropium: 2 RCTs; 823 people; RR 0.78, 95% CI 0.63 to 0.95). It found that tiotropium significantly improved health related quality of life compared with placebo at 13–52 weeks (3 RCTs; 2751 people; mean change in St George's Respiratory Questionnaire: -2.9, 95% CI -4.3 to -1.5). One included RCT found that tiotropium significantly improved mean trough FEV₁ compared with placebo and 24 hours after dosing (mean improvement compared with placebo at 3 hours: 140–220 mL; P value not reported; at 24 hours: 120–220 mL; P < 0.01).²⁵ One included RCT found that tiotropium significantly improved trough FEV₁ compared with ipratropium at 1 year (improvement in FEV₁ with tiotropium v ipratropium: 150 mL; P < 0.001).²⁶ One of the references in the review²² reported results from two 6 month RCTs, one of which was also reported in another reference included in the review;^{23,24} however, the review used both references in the meta-analysis. The additional RCT compared three interventions over a 5 year period: an intensive 12 session smoking cessation programme combining behaviour modification and use of nicotine gum; the same smoking intervention programme plus ipratropium three times daily; or usual care.¹⁰ For results of the smoking cessation programme, see benefits of psychosocial plus pharmacological interventions for smoking cessation, p 17. Although the decline in FEV₁ was significantly slower in people in both smoking cessation groups compared with usual care, adding ipratropium had no significant effect (5887 smokers aged 35–60 years with spirometric signs of early chronic obstructive pulmonary disease; FEV₁ 75% predicted; 5 year mean cumulative decline in FEV₁ before bronchodilator: usual care 249 mL, 95% CI 236 mL to 262 mL; smoking programme plus ipratropium 188 mL, 95% CI 175 mL to 200 mL; smoking programme plus placebo 172 mL, 95% CI 159 mL to 185 mL). **Inhaled anticholinergics plus beta₂ agonists:** See benefits of inhaled anticholinergics plus beta₂ agonists, p 8. **Inhaled anticholinergics versus beta₂ agonists:** See benefits of inhaled anticholinergics versus beta₂ agonists, p 9.

Harms:

Short term short acting anticholinergics: One RCT comparing ipratropium found similar rates of adverse effects with ipratropium and placebo.¹⁹ **Long term treatment with ipratropium or tiotropium:** The review did not report on adverse effects. The first included RCT comparing tiotropium versus placebo found similar rates of adverse effects, except for dry mouth (16.0% with tiotropium v 2.7% with placebo; P < 0.05).²⁵ The second included RCT found that dry mouth was significantly more common with tiotropium compared with ipratropium (12.1% with tiotropium v 6.1% with ipratropium; P < 0.05).²⁶ The third included paper of two RCTs found that tiotropium significantly increased the proportion of people who had dry mouth compared with placebo (8.2% with tiotropium v 2.3% with placebo; reported as significant, P value not reported).^{22,23} The fifth included RCT found that tiotropium increased the proportion of people who had dry mouth compared with ipratropium, but the difference was not significant (dry mouth: 28/191 [14.7%] v 10/97 [10.3%]; difference reported as non-significant).²⁷ The additional RCT of long term treatment found no significant difference between ipratropium and placebo in serious adverse events (cardiac symptoms, hypertension, skin rashes, and urinary retention: 1.2% with ipratropium v 0.8% with placebo), and dry mouth was the most common mild adverse effect.¹⁰ **Inhaled anticholinergics plus beta₂ agonists:** See harms of inhaled anticholinergics plus beta₂ agonists, p 8. **Inhaled anticholinergics versus beta₂ agonists:** See harms of inhaled anticholinergics versus beta₂ agonists, p 9.

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Comment: RCTs of long term treatment found no evidence that people developed tachyphylaxis in response to the bronchodilating effect of ipratropium or tiotropium over a 1–5 year period.^{10,25} The review included any RCTs with treatment for over 3 months, whereas our inclusion criteria for long term treatment is over 6 months.²¹ However, we have presented the results of the review, because only one of the included RCTs was of a treatment duration significantly shorter than 6 months.

OPTION INHALED BETA₂ AGONISTS

RCTs found that treatment with inhaled beta₂ agonists for 1 week to 12 months improved forced expiratory volume in 1 second compared with placebo. A systematic review and RCTs found that long acting beta₂ agonists for 12–52 weeks improved quality of life and exacerbation rates compared with placebo.

Benefits: **Short term treatment with short acting beta₂ agonists:** We found one systematic review (search date 2002, 9 crossover RCTs, 264 people with stable chronic obstructive pulmonary disease [COPD]) comparing short acting beta₂ agonists versus placebo for at least 1 week.²⁸ It found that beta₂ agonists delivered by metered dose inhaler slightly but significantly increased forced expiratory volume in 1 second (FEV₁) compared with placebo (WMD 0.14 L, 95% CI 0.04 L to 0.25 L), and significantly improved daily breathlessness score (results reported as SMD; P < 0.001). There was no significant difference between treatments in exercise tolerance (4 RCTs; SMD + 0.18, 95% CI -0.11 to + 0.47), although the trials were small and the results were heterogeneous. The meta-analysis used post-crossover results, but there is unlikely to be persistence of treatment effects after crossover because the treatment is short acting. **Short term treatment with long acting beta₂ agonists:** We found one systematic review,²¹ one additional RCT,²⁹ and two subsequent RCTs.^{30,31} The review found that beta₂ agonists significantly reduced COPD exacerbations and improved health related quality of life compared with placebo at 12–52 weeks (search date 2002, publication date of some studies 2003; exacerbations: 8 RCTs; 3872 people; RR 0.79, 95% CI 0.69 to 0.90; mean change in St George's Respiratory Questionnaire: 5 RCTs; 2551 people; -2.8, 95% CI -4.1 to -1.6). The effect on FEV₁ was variable (data not reported). The review did not investigate the effects of long acting beta₂ agonists on exercise capacity; however, four RCTs reported on exercise capacity, using varying inclusion criteria and methodologies.^{19,29–31} One RCT included in the review compared three treatments: formoterol 18 µg twice daily, ipratropium, and placebo.¹⁹ It found no significant difference between formoterol and placebo in the shuttle walking test after 12 weeks' treatment (183 people with moderate to severe COPD; increase from baseline: 20.4 m with formoterol v 6.0 m with placebo; reported as non-significant, P value not reported, baseline mean distance 325 m). The additional RCT compared the effects of three interventions on exercise capacity: formoterol (4.5, 9, or 18 µg twice daily), ipratropium (80 µg 3 times daily), or placebo for 1 week.²⁹ It found that formoterol and ipratropium slightly but significantly increased time to exhaustion compared with placebo (34 people; crossover design; 10.94 minutes with 4.5 µg formoterol; 10.20 minutes with placebo; P < 0.0001 v placebo; 10.78 minutes with 9 µg formoterol; P < 0.01 v placebo; 10.59 minutes with 18 µg formoterol; P < 0.05 v placebo; 10.98 minutes with ipratropium; P < 0.0001 v placebo).²⁹ The first subsequent RCT compared 18 µg tiotropium versus placebo once daily for 42 days. It found that tiotropium significantly increased post-dose exercise endurance time compared with placebo (187 people with moderate to severe COPD [FEV₁ 44% predicted]; difference in exercise endurance time: 105 seconds; P = 0.01).³⁰ The second subsequent RCT compared inhaled salmeterol 50 µg versus placebo twice daily for 2 weeks. It found that salmeterol significantly increased peak exercise endurance compared with placebo (23 people with moderate to severe COPD [mean FEV₁ 42% predicted]; crossover design; difference in peak exercise endurance time: 96 seconds; P = 0.02).³¹ **Long term treatment with beta₂ agonists:** We found no systematic review of long term treatment with short or long acting beta₂ agonists versus placebo. We found eight RCTs (7 publications).^{22,23,32–36} The first RCT (623 people) compared salmeterol 50 µg twice daily, tiotropium, and placebo for 6 months.²³ It found that salmeterol significantly improved mean pre-dose morning FEV₁ and average FEV₁ (0–12 hours after dose) compared with placebo (mean improvement in mean pre-dose morning FEV₁ 85 mL; P < 0.0001; mean improvement

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in average FEV₁ 138 mL; P < 0.0001). However, the RCT found no significant improvement in symptom score (difference in transition dyspnoea index focal score: 0.24 U; P = 0.56) or health related quality of life score (mean change in St George's Respiratory Questionnaire: -3.54 with salmeterol v -2.43 with placebo; P = 0.39) compared with placebo. A second article combined results from two RCTs (1207 people) comparing salmeterol 50 µg twice daily, tiotropium 18 µg once daily, and placebo over 24 weeks.²² It found that salmeterol significantly improved pre-dose FEV₁ compared with placebo (difference: 90 mL; P < 0.01). It found no significant difference between treatments in exacerbation rate or quality of life (exacerbations: 1.23 per person per year with salmeterol v 1.49 per person per year with placebo; improvement in St George's Respiratory Questionnaire: 2.8 with salmeterol v 1.5 with placebo; reported as non-significant for both outcomes, P values not reported). The fourth and fifth RCTs compared the same four treatments twice daily: salmeterol 50 µg alone, salmeterol plus fluticasone 500 µg, fluticasone alone, and placebo.^{32,33} The fourth RCT (691 people) found that salmeterol significantly increased pre-dose and post-dose FEV₁ compared with placebo at 24 weeks (pre-dose increase: 92 mL; P < 0.05; post-dose increase: 191 mL; P < 0.01).³² It found no significant difference between salmeterol and placebo in dyspnoea or quality of life (difference in Transitional Dyspnoea Index: 0.5; Chronic Respiratory Disease Questionnaire score: 3.8; reported as non-significant, P value not reported). The fifth RCT (1465 people) found that salmeterol significantly improved pre-dose FEV₁ and significantly reduced the exacerbation rate at 1 year compared with placebo (FEV₁: 1323 mL with salmeterol v 1264 mL with placebo; P < 0.0001; exacerbation rate: 1.04 per person per year with salmeterol v 1.30 per person per year with placebo; P = 0.0003).³³ It found no significant difference between treatments in quality of life (St George's Respiratory Questionnaire score: 45.2 with salmeterol v 46.3 with placebo; reported as non-significant, P value not reported). The sixth RCT (723 people) compared salmeterol 50 µg, fluticasone 250 µg, salmeterol plus fluticasone, and placebo for 24 weeks.³⁵ It found that salmeterol significantly increased 2 hour post-dose FEV₁ and significantly improved Transitional Dyspnoea Index compared with placebo at 24 weeks (FEV₁: increase 140 mL; P < 0.001; Transitional Dyspnoea Index: difference 0.7; P < 0.05). It found no significant difference in health related quality of life (Chronic Respiratory Disease Questionnaire score: difference 2.0; P > 0.05).³⁵ The seventh RCT (812 people, FEV₁ 36% predicted) compared four treatments twice daily for 1 year: formoterol 12 µg alone, formoterol plus budesonide, budesonide alone, and placebo.³⁴ It found that formoterol significantly increased post-dose FEV₁ compared with placebo. It found no significant difference in severe exacerbations (increase in FEV₁: 14%, 95% CI 10% to 18%; reduction in exacerbations: 25%, 95% CI -26% to + 23%). The eighth RCT (1022 people) compared four inhaled treatments twice daily for 1 year: formoterol 9 µg, budesonide 320 µg plus formoterol 9 µg, budesonide alone 400 µg, and placebo.³⁶ It found that formoterol significantly improved FEV₁ compared with placebo after 1 year. It found no significant difference in exacerbation rates (FEV₁: increase 85 mL; P < 0.001; exacerbations: 1.85 per person per year with formoterol v 1.80 per person per year with placebo; difference 0.05 per person per year; P = 0.828). **Inhaled anticholinergics plus beta₂ agonists:** See benefits of anticholinergics plus beta₂ agonists, p 8. **Inhaled anticholinergics versus beta₂ agonists:** See benefits of inhaled anticholinergics versus beta₂ agonists, p 9. **Inhaled corticosteroids plus long acting beta₂ agonists:** See benefits of inhaled corticosteroids plus long acting beta₂ agonists, p 12.

Harms:

In people with asthma, beta₂ agonists have been linked to increased risk of death, worsened control of asthma, and deterioration in lung function.³⁷ One systematic review found that, in people with asthma or COPD, beta₂ agonists significantly increase the risk of adverse cardiovascular events compared with placebo (search date 2003; 20 RCTs; 6623 people with asthma or COPD; RR 2.54, 95% CI 1.59 to 4.05).⁴⁰ A single dose of beta₂ agonist significantly increased heart rate and reduced serum potassium concentration compared with placebo (heart rate: 11 RCTs; 386 people with asthma or COPD; WMD 9.12, 95% CI 5.32 to 12.92; reduced serum potassium: 6 RCTs; 168 people with asthma or COPD; WMD -0.36, 95% CI -0.54 to -0.18).⁴⁰ One crossover RCT (53 people with COPD, FEV₁ < 70% predicted) compared regular versus as needed treatment with the short acting inhaled beta₂ agonist salbutamol for 3 months.³⁸ It found that regular salbutamol doubled the total daily amount of salbutamol used

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compared with as needed (13 puffs/day [of which 8 puffs were the allocated regular dose] with regular v 6 puffs/day with as needed treatment; significance not reported), with no significant difference in symptoms or lung function. The RCT used post-crossover results, but there is unlikely to be persistence of treatment effects after crossover because the treatment is short acting. The most common immediate adverse effect is tremor, which is usually worse in the first few days of treatment. High doses of beta₂ agonists can reduce plasma potassium, cause dysrhythmia, and reduce arterial oxygen tension.³⁹ The risk of adverse events may be higher in people with pre-existing cardiac arrhythmias and hypoxaemia.⁴¹ The RCTs comparing salmeterol or formoterol with placebo found no significant increase in adverse effects.^{16,17,19,22,32-36} The reviews did not report on harms.^{21,28} **Inhaled anticholinergics plus beta₂ agonists:** See harms of inhaled anticholinergics plus beta₂ agonists, p 8. **Inhaled anticholinergics versus beta₂ agonists:** See harms of inhaled anticholinergics versus beta₂ agonists, p 9. **Inhaled corticosteroids plus long acting beta₂ agonists:** See harms of inhaled corticosteroids plus long acting beta₂ agonists, p 13.

Comment: None.

OPTION INHALED ANTICHOLINERGICS PLUS BETA₂ AGONISTS

A systematic review found that combining a short acting beta₂ agonist with an anticholinergic drug (ipratropium) for 12 weeks improved exacerbations compared with the beta₂ agonist alone but not ipratropium alone. One RCT found that combining a long acting beta₂ agonist with an anticholinergic drug did not improve symptoms but modestly improved some measures of lung function compared with the long acting beta₂ agonist alone. One RCT found that, when combined with an anticholinergic drug, a long acting beta₂ agonist improved forced expiratory volume in 1 second and peak expiratory flow more than a short acting beta₂ agonist. We found no RCTs of long term treatment comparing anticholinergics plus beta₂ agonists with placebo.

Benefits: We found no systematic review. **Short term treatment with anticholinergics plus short acting inhaled beta₂ agonists:** We found one systematic review,²¹ which found that anticholinergics plus short acting beta₂ agonists significantly reduced chronic obstructive pulmonary disease exacerbations compared with beta₂ agonists alone at 12 weeks (search date 2002; 3 RCTs; 1399 people; RR 0.68, 95% CI 0.51 to 0.91). It found no significant difference in chronic obstructive pulmonary disease exacerbations between anticholinergics plus beta₂ agonists and ipratropium alone at 12 weeks (2 RCTs; 1186 people; RR 1.04, 95% CI 0.65 to 1.68).²¹ **Short term treatment with anticholinergics plus long acting inhaled beta₂ agonists:** One RCT (94 people) compared the long acting beta₂ agonist salmeterol (50 µg twice daily) plus ipratropium (40 µg 4 times daily) versus salmeterol alone (50 µg twice daily) for 12 weeks.⁴² It found that the combination significantly improved forced expiratory volume in 1 second (FEV₁) compared with the beta₂ agonist alone (mean improvement as a percentage of predicted FEV₁: 8% with combination v 5% with beta₂ agonist alone; P < 0.01), and evening but not morning peak expiratory flow[Ⓞ]. It found no significant difference in daytime or night time symptoms.⁴³ **Short term treatment with anticholinergics plus long acting beta₂ agonists versus anticholinergics plus short acting beta₂ agonists:** One crossover RCT (172 people) compared ipratropium (40 µg 4 times daily) plus formoterol (12 µg twice daily) versus ipratropium (40 µg 4 times daily) plus salbutamol (200 µg 4 times daily) for 6 weeks.⁴⁴ It found that formoterol plus ipratropium significantly improved FEV₁ and peak expiratory flow from baseline after 3 weeks of treatment compared with salbutamol plus ipratropium (improvement in mean morning peak expiratory flow from baseline over the previous 7 days with formoterol: 12 L/minute, 95% CI 6 L/minute to 19 L/minute; improvement in pre-medication FEV₁ from baseline: 116 mL, 95% CI 83 mL to 150 mL). **Long term treatment with anticholinergics plus inhaled beta₂ agonists:** We found no RCTs of long term treatment with anticholinergics plus beta₂ agonists compared with placebo.

Harms: The RCTs found no significant differences in adverse effects between treatments.⁴²⁻⁴⁹

Comment: None.

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OPTION INHALED ANTICHOLINERGICS COMPARED WITH BETA₂ AGONISTS

RCTs found inconsistent evidence about the effects of short acting inhaled anticholinergics compared with long acting beta₂ agonists for up to 3 months. Two RCTs identified by a systematic review found that 6 months of a long acting inhaled anticholinergic improved forced expiratory volume in 1 second compared with a long acting inhaled beta₂ agonist. The RCTs found mixed results for health related quality of life and one of the RCTs found no significant difference between a long acting inhaled anticholinergic and a long acting inhaled beta₂ agonist in quality of life or exacerbation rates at 6 months.

Benefits: **Short term treatment:** We found one non-systematic review (7 RCTs, 1445 people)⁵⁰ and three subsequent RCTs^{16–18} comparing ipratropium versus different length acting beta₂ agonists for 90 days. The review found that ipratropium significantly improved mean forced expiratory volume in 1 second (FEV₁) compared with short acting beta₂ agonists (28 mL increase with ipratropium v 1 mL decrease with beta₂ agonist, CI not reported; P < 0.05). The first two subsequent RCTs compared ipratropium (36 µg 4 times daily) versus salmeterol (42 µg twice daily).^{16,17} The first RCT (411 people) found that salmeterol significantly improved average FEV₁ at 4 and 8 weeks compared with ipratropium (P < 0.005), but not immediately after treatment or at 12 weeks.¹⁶ The second RCT (405 people) found no significant difference in FEV₁ between treatments at any time (P > 0.097).¹⁷ The third RCT (780 people) compared four treatments: ipratropium, formoterol 12 µg twice daily, formoterol 24 µg twice daily, or placebo for 12 weeks.¹⁸ It found that both doses of formoterol significantly improved FEV₁ compared with ipratropium (improvement in average FEV₁ over 12 hours after medication with 12 µg formoterol v ipratropium: 86 mL, 95% CI 37 mL to 136 mL; with 24 µg formoterol v ipratropium: 57 mL, 95% CI 7 mL to 106 mL). Lower dose, but not higher dose, formoterol improved quality of life scores compared with ipratropium (improvement in total score on St George's Respiratory Questionnaire with 12 µg formoterol 3.79; P < 0.001; with 24 µg formoterol about 2, difference presented graphically; P = 0.102). **Long term treatment:** We found one systematic review (search date 2002, 2 RCTs) comparing long term treatment with anticholinergics versus beta₂ agonists.²¹ The two RCTs compared the same three treatments over 6 months: tiotropium 18 µg daily, salmeterol 50 µg twice daily, or placebo.^{22,23} The review found that tiotropium improved trough FEV₁ compared with salmeterol at 6 months; difference 37 mL, 95% CI 12 mL to 61 mL.²¹ The first RCT (623 people) found that tiotropium significantly improved mean pre-dose morning FEV₁, average FEV₁, and health related quality of life compared with salmeterol (improvement in mean pre-dose morning FEV₁ 140 mL with tiotropium v 90 mL with salmeterol; P < 0.01; average FEV₁ [0–12 hours after the dose] 80 mL greater with tiotropium; P < 0.001; AR for 4 unit improvement in health related quality of life [St George's Respiratory questionnaire] 51% with tiotropium v 40% with salmeterol; P < 0.05).²³ The second RCT (1207 people, half of whom were included in the first RCT²³) found that tiotropium led to a small but significant increase in pre-dose FEV₁ compared with salmeterol (increase in pre-dose FEV₁: 120 mL with tiotropium v 90 mL with salmeterol; P < 0.05).²² Over a period of 6 months, the improvements in FEV₁ were maintained with tiotropium but not completely maintained with salmeterol (data not reported). The RCT found no significant difference between the two active treatments in exacerbation rates, hospitalisations, or quality of life (exacerbations: 1.07 per person per year with tiotropium v 1.23 with salmeterol; P = 0.22; hospitalisation: 0.43 per person per year with tiotropium v 0.65 with salmeterol; increase in St George's Respiratory Questionnaire: 4.2 with tiotropium v 2.8 with salmeterol; reported as non-significant, P value not reported).

Harms: Adverse effects such as tremor and dysrhythmia associated with beta₂ agonists seem to be more frequent than the adverse effects associated with anticholinergics, although the review provided no evidence for this.⁵⁰ The RCTs comparing salmeterol with ipratropium found no significant difference in the frequency of adverse effects.^{16,17} In the first RCT of long term treatment, dry mouth was more frequent with tiotropium than with salmeterol

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or placebo (experienced by 10% with tiotropium, no further data reported).²³ The second RCT of long term treatment also found that tiotropium significantly increased dryness of the mouth compared with salmeterol (8.2% with tiotropium v 1.7% with salmeterol; reported as significant, P value not reported).²² It found no significant difference between the treatments in other adverse effects.

Comment: It has been suggested that older people experience a greater bronchodilator response with anticholinergic drugs than with beta₂ agonists, but we found no evidence for this.

OPTION THEOPHYLLINES

One systematic review found that theophyllines slightly improved forced expiratory volume in 1 second compared with placebo after 3 months. One large RCT found that theophyllines improved forced expiratory volume in 1 second compared with placebo after 12 months' treatment. The usefulness of these drugs is limited by adverse effects and the need for frequent monitoring of blood concentrations.

Benefits: **Short term treatment:** We found one systematic review (search date 2002, 20 small RCTs, 442 people) comparing theophyllines versus placebo for 1 week to 3 months.⁵¹ It found that theophyllines slightly but significantly improved forced expiratory volume in 1 second \oplus (FEV₁) compared with placebo (WMD 100 mL, 95% CI 40 mL to 160 mL). It found no significant difference in maximum walking distance (results presented as SMD).⁵¹ **Long term treatment:** We found one RCT (854 people) comparing four treatments: open label theophylline, double blinded formoterol 12 µg twice daily, formoterol 24 µg twice daily, or placebo for 12 months.⁵² It found that theophylline significantly improved FEV₁ compared with placebo (mean difference in FEV₁ with theophylline v placebo + 120 mL, CI not reported; P < 0.001).

Harms: **Short term treatment:** The RCTs identified by the review did not report adverse effects.⁵¹ The therapeutic range for theophyllines is small, with blood concentrations of 10–15 mg/L required for optimal effects. Well documented adverse effects include nausea, diarrhoea, headache, irritability, seizures, and cardiac arrhythmias. These may occur within the therapeutic range.⁵³ **Long term treatment:** The RCT found that people receiving theophylline were twice as likely to discontinue treatment compared with those taking placebo (P < 0.002).⁵² Nausea was the most frequent adverse effect.

Comment: None.

OPTION ORAL CORTICOSTEROIDS

We found no RCTs on long term benefits. One systematic review found that treatment with oral corticosteroids for 2–4 weeks improved forced expiratory volume in 1 second compared with placebo. Long term systemic corticosteroids are associated with serious adverse effects, including osteoporosis and diabetes.

Benefits: **Short term treatment:** We found one systematic review (search date 1989, 10 RCTs, 445 people), which compared oral corticosteroids versus placebo in people with stable chronic obstructive pulmonary disease.⁵⁴ Treatment usually lasted 2–4 weeks. It found that oral corticosteroids significantly increased the proportion of people with a 20% or greater improvement in baseline forced expiratory volume in 1 second \oplus compared with placebo (WMD 10%, 95% CI 2% to 18%). When five RCTs not meeting all quality criteria were included in the analysis, the difference in effect size was 11% (95% CI 4% to 18%). **Long term treatment:** We found no long term RCTs examining the effects of oral steroids on decline in lung function.

Harms: Many reviews have described the considerable harms of systemic corticosteroids, including osteoporosis and induction of diabetes.⁵⁵

Comment: None.

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OPTION INHALED CORTICOSTEROIDS

RCTs found no significant difference between inhaled corticosteroids and placebo in lung function (forced expiratory volume in 1 second) over 10 days to 10 weeks. One systematic review and one subsequent RCT found no significant difference in decline in forced expiratory volume in 1 second between inhaled corticosteroids and placebo after 24 months. However, a second systematic review that examined effects of high dose inhaled corticosteroids and four subsequent RCTs found that inhaled corticosteroids slightly reduced the decline in forced expiratory volume in 1 second compared with placebo after 12–24 months. Two systematic reviews and one subsequent RCT found that long term inhaled steroids reduced the frequency of exacerbations compared with placebo. Two subsequent RCTs found no significant difference in exacerbation rates. Long term inhaled steroids may predispose to adverse effects, including skin bruising and oral candidiasis.

Benefits:

Short term treatment: We found no systematic review. We found one non-systematic review, which identified 10 RCTs of less than 6 months' duration.⁵⁶ Nine short term trials (10 days to 10 weeks, 10–127 people) found no significant difference between inhaled steroids and placebo in improvement in lung function (forced expiratory volume in 1 second \odot [FEV₁]). **Long term treatment:** We found two systematic reviews examining the effect of inhaled steroids on decline in FEV₁,^{57,58} two systematic reviews examining the effect of inhaled steroids on exacerbations,^{21,59} and five subsequent RCTs.^{32–36} The first systematic review compared the effects of any dose of inhaled corticosteroids versus placebo on FEV₁.⁵⁷ It found no significant difference between inhaled corticosteroids and placebo in the rate of decline of FEV₁ (search date 2002; 6 RCTs with follow up \geq 24 months; 3571 people; reduction in annual decline in FEV₁ for corticosteroid v placebo: + 5 mL, 95% CI –1.2 mL to + 11.2 mL). The second systematic review (search date 2003, 4 RCTs all of which were included in the first systematic review, 2416 people) compared the effects of high dose inhaled corticosteroids versus placebo on FEV₁.⁵⁸ It found that high dose inhaled corticosteroids significantly reduced decline in lung function compared with placebo after 24 months; reduction in annual decline in FEV₁ with high dose inhaled corticosteroids v placebo: 9.9 mL, 95% CI 2.3 mL to 17.5 mL). The third systematic review (search 2001; 9 RCTs of at least 6 months' duration; 3976 people found that inhaled corticosteroids significantly reduced exacerbations compared with placebo; RR 0.70, 95% CI 0.58 to 0.84).⁵⁹ The fourth systematic review (search date 2002; 6 RCTs, five of which were also in the third systematic review;⁵⁹ 1741 people with stable moderate to severe COPD) found that inhaled corticosteroids significantly reduced chronic obstructive pulmonary disease (COPD) exacerbations compared with placebo; RR 0.76, 95% CI 0.72 to 0.80.²¹ The five subsequent RCTs all compared four treatments: combination treatment with inhaled corticosteroids plus long acting beta₂ agonist, inhaled steroids alone, inhaled beta₂ agonists alone, and placebo.^{32–36} The first subsequent RCT (691 people) found that 500 μ g fluticasone significantly improved FEV₁ and dyspnoea compared with placebo at 6 months (difference between fluticasone and placebo in FEV₁: 105 mL; P < 0.05; difference in Transitional Dyspnoea Index: 1.0; P < 0.05).³² The second subsequent RCT (1465 people) found that fluticasone significantly improved pre-dose FEV₁ and exacerbation rates compared with placebo at 1 year (FEV₁: 1302 mL with fluticasone v 1264 mL with placebo; P < 0.0001; exacerbation, mean per person per year: 1.05 with fluticasone v 1.30 with placebo; P = 0.003).³³ It found no significant difference between fluticasone and placebo in quality of life or symptoms (St George's Respiratory Questionnaire: 45.5 with fluticasone v 46.3 with placebo; reported as non-significant, P value not reported). The third subsequent RCT (812 people) found that budesonide 400 μ g twice daily significantly increased FEV₁ compared with placebo at 1 year (difference: 5%, 95% CI 2% to 9%).³⁴ It found no significant difference between budesonide and placebo in exacerbation rate or quality of life (reduction in exacerbations: + 15%, 95% CI –10.3% to + 34.1%; change in St George's Respiratory Questionnaire: –1.9 with budesonide v –0.03 with placebo). The fourth subsequent RCT (1022 people) found no significant difference between budesonide and placebo in time to first exacerbation or decline in FEV₁ at 1 year (median time to first exacerbation: 178 days with budesonide v 96 days with placebo; P = 0.80; decline in FEV₁ at 1 year: results presented graphically; P = 0.145 for difference; CI not reported). However, it

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found that budesonide significantly improved health related quality of life compared with placebo at 1 year (mean change in St George's Respiratory Questionnaire score from baseline: about 0 with budesonide v about -3 with placebo; $P < 0.05$; CI not reported).³⁶ The fifth subsequent RCT (723 people) found that fluticasone increased post-dose FEV₁ and health related quality of life compared with placebo after 24 weeks (increase in FEV₁ from baseline: 147 mL with fluticasone v 58 mL with placebo; $P < 0.048$; improvement in Chronic Respiratory Disease Questionnaire score from baseline: 10.4 with fluticasone v 5.0 with placebo; $P = 0.002$; CI not reported).³⁵ However, it found no significant difference in symptoms at 24 weeks (mean Transitional Dyspnoea Index score: 1.7 with fluticasone v 1.0 with placebo; $P = 0.057$). **Inhaled corticosteroids plus long acting beta₂ agonists:** See benefits of inhaled corticosteroids plus long acting beta2 agonists, p 12.

Harms:

Short term treatment: The non-systematic review gave no information on adverse effects.⁵⁶ **Long term treatment:** The first and second reviews did not report on harms.^{57,58} The third review found that inhaled corticosteroids significantly increased the risks of oropharyngeal candidiasis and skin bruising compared with placebo (candidiasis: RR 2.1, 95% CI 1.5 to 3.1; skin bruising RR 2.1, 95% CI 1.6 to 2.8).⁵⁹ The fourth systematic review found that corticosteroids significantly increased oral thrush, dysphonia, and bruising compared with placebo, and it found no significant difference in cataracts (oral thrush: 6 RCTs; 5562 people; RR 2.98, 95% CI 2.09 to 4.26; dysphonia: 4 RCTs; 3772 people; RR 2.02, 95% CI 1.43 to 2.83; bruising: 3 RCTs; 3332 people; RR 1.62, 95% CI 1.18 to 2.22; cataracts: 2 RCTs; 1867 people; RR 1.05, 95% CI 0.84 to 1.31).²¹ The review found that corticosteroids reduced bone mineral density in the femoral neck and lumbar spine compared with placebo over 3–4 years (1 RCT of inhaled triamcinolone; 972 people; reduction in bone mineral density: femoral neck: 1.57%, 95% CI 2.40% to 0.74%; lumbar spine: 1.07%, 95% CI 1.86% to 0.28%).²¹ The review found no excess risk of fractures with corticosteroids over 3 years (1 RCT; 972 people; RR 0.70, 95% CI 0.36 to 1.37).^{21,60} The lifetime risk of fractures in people who take corticosteroids for longer than 3–4 years is not known. The first subsequent RCT found that more people taking fluticasone than taking placebo had oropharyngeal candidiasis but found that other adverse effects were similar between treatments (candidiasis: 10% with fluticasone v < 1% with placebo; P value not reported).³² The second subsequent RCT found that fluticasone increased oropharyngeal candidiasis compared with placebo but found that other adverse effects were similar between treatments (candidiasis: 7% with fluticasone v 2% with placebo; P value not reported).³³ The third subsequent RCT found no significant difference between budesonide 400 µg twice daily and placebo in adverse effects.³⁴ The fourth RCT reported that adverse event rates were similar among all treatment groups (P values not reported),³⁶ and the fifth RCT reported that serious adverse event rates and rates of adverse events leading to withdrawal of treatment were similar among all treatment groups (serious adverse event rate about 5% in all groups; rate of adverse events leading to withdrawal about 5% in all groups; P values not reported).³⁵ **Inhaled corticosteroids plus long acting beta₂ agonists:** See harms of inhaled corticosteroids plus long acting beta2 agonists, p 13.

Comment:

The studies of inhaled corticosteroids have been performed in people with moderate to severe disease (FEV₁ < 50% predicted) and hence apply to that population. The Global Initiative on Obstructive Pulmonary Disease has therefore advocated the use of inhaled corticosteroids only in people with an FEV₁ less than 50% predicted and frequent exacerbations (at least 3 exacerbations in the last 3 years).¹

OPTION

INHALED CORTICOSTEROIDS PLUS LONG ACTING BETA₂ AGONISTS

RCTs found that the combination of an inhaled corticosteroid plus a long acting beta₂ agonist reduced exacerbation rates and improved lung function, symptoms, and health related quality of life compared with placebo in people with moderate to severe disease. In general, the combination was more effective than inhaled corticosteroid alone or long acting beta₂ agonist alone, although this difference was not significant for all outcomes.

Benefits:

We found one systematic review (search date 2004, 3 RCTs, 3299 people with moderate to severe disease), which compared four treatments: inhaled corticosteroid alone; an inhaled long acting beta₂ agonist alone; an inhaled corticosteroid plus a long

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acting beta₂ agonist (combined in 1 inhaler); and placebo.⁶¹ It found that combination therapy significantly reduced chronic obstructive pulmonary disease exacerbations compared with placebo and beta₂ agonists alone, and it found no significant difference between combination therapy and corticosteroids alone; versus placebo: 3 RCTs; 1642 people with moderate to severe chronic obstructive pulmonary disease; RR 0.76, 95% CI 0.68 to 0.84; versus beta₂ agonist alone: 3 RCTs; 1648 people; RR 0.85, 95% CI 0.77 to 0.95; versus corticosteroid alone: 3 RCTs; 1649 people; RR 0.91, 95% CI 0.81 to 1.02). The review did not present a meta-analysis of quality of life data. The RCTs identified by the review found that combination therapy significantly improved health related quality of life compared with placebo (Chronic Respiratory Disease Questionnaire: 1 RCT; difference 5.3; P < 0.05; 1 RCT; adjusted mean difference 5.2; P ≤ 0.048; St George's Respiratory Questionnaire: 1 RCT; 44.1 with combination v 46.3 with placebo; difference -2.2, 95% CI -3.3 to -1.0; 1 RCT; reduction from baseline: -3.9 with combination v -0.03 with placebo; P = 0.009; 1 RCT; results presented graphically; P < 0.001).³²⁻³⁶ The RCTs identified by the review found that combination therapy improved health related quality of life compared with corticosteroids alone, although the difference was only significant in two RCTs (Chronic Respiratory Disease Questionnaire: 1 RCT; difference 4.8 v fluticasone; P < 0.05; 1 RCT; adjusted mean difference -0.6 v fluticasone; P > 0.048; St George's Respiratory Questionnaire: 1 RCT; 44.1 with combination v 45.5 with fluticasone; difference -1.4, 95% CI -2.5 to -0.2; 1 RCT; reduction from baseline: -3.9 with combination v -1.9 with budesonide; significance not reported; 1 RCT; results presented graphically; P = 0.001 v budesonide).³²⁻³⁶ The RCTs identified by the review found that combination therapy improved health related quality of life compared with beta₂ agonists alone, although the difference was only significant in one RCT (Chronic Respiratory Disease Questionnaire: 1 RCT; difference 1.6 v salmeterol; reported as non-significant; 1 RCT; adjusted mean difference 3.2 v salmeterol; P > 0.048; St George's Respiratory Questionnaire: 1 RCT; 44.1 with combination v 45.2 with salmeterol; difference -1.1, 95% CI -2.2 to +0.1; 1 RCT; reduction from baseline: -3.9 with combination v -3.6 with formoterol; significance not reported; 1 RCT; results presented graphically; P = 0.014 v formoterol).³²⁻³⁶ The review did not present meta-analysis of all RCTs for changes in pre-dose forced expiratory volume in 1 second (FEV₁). Two RCTs identified by the review found that combination therapy significantly improved pre-dose FEV₁ compared with placebo, fluticasone, and salmeterol (versus placebo: 2 RCTs; 697 people; WMD 0.16 L, 95% CI 0.12 L to 0.20 L; versus fluticasone: 2 RCTs; 690 people; WMD 0.05 L, 95% CI 0.02 L to 0.09 L; versus salmeterol: 2 RCTs; 677 people; WMD 0.06 L, 95% CI 0.02 L to 0.10 L). Two RCTs identified by the review found that combination therapy significantly improved pre-dose FEV₁ compared with placebo and budesonide (versus placebo: 2 RCTs; 923 people; percentage increase in FEV₁ 14.40%, 95% CI 11.91% to 16.90%; versus budesonide: 2 RCTs; 917 people; percentage increase in FEV₁ 10.17%, 95% CI 7.71% to 12.62%). Meta-analysis of placebo and budesonide comparisons was done using a fixed effects model. However, the formoterol comparison was analysed using a random effects model because of heterogeneity between studies. This analysis found no significant difference between combination therapy compared with formoterol alone (2 RCTs; 918 people; percentage increase in FEV₁ + 3.06%, 95% CI -0.86% to + 6.97).

Harms:

The first RCT in the review found that more people having combination treatment or fluticasone alone had candidiasis than people taking placebo (7% with combination v 10% with fluticasone v < 1% with placebo and salmeterol; P value not reported).³² Other adverse effect rates were similar among treatment groups. The second RCT in the review found a slightly lower rate of candidiasis (6% with combination v 6% with fluticasone v 1% with placebo and salmeterol; P value not reported).³³ It too found similar rates of other adverse effects among treatment groups. The third RCT in the review found similar rates of adverse effects among treatment groups but did not specifically report candidiasis rate.³⁴ Two RCTs in the review found no clinically relevant decreases in serum cortisol with fluticasone alone or combination treatment.^{33,34} The fourth RCT in the review reported that adverse events rates were similar among all treatment groups (P values not reported),³⁶ and the fifth RCT in the review reported that serious adverse event rates and rates of adverse events leading to withdrawal of treatment were similar among all treatment groups (serious adverse event rate and rate of adverse events leading to withdrawal about 5% in all groups; P values not reported).³⁵

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Comment: These studies have been performed 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 beta₂ agonists only in people with an FEV_1 less than 50% predicted and frequent exacerbations (i.e. at least 3 in the last 3 years).¹ The review included one RCT that does not meet *Clinical Evidence* inclusion criteria for sample size. The review did not include it in the meta-analysis, and we have not reported separate results.⁶²

OPTION MUCOLYTIC DRUGS

Two systematic reviews in chronic bronchitis found limited evidence that mucolytics for 3–24 months reduced the frequency and duration of exacerbations compared with placebo. Two RCTs in chronic obstructive pulmonary disease found no significant difference in decline in forced expiratory volume in 1 second and exacerbations.

Benefits: **Long term treatment:** We found two systematic reviews,^{63,64} and two subsequent RCTs.^{65,66} Not all participants included in the reviews had chronic obstructive pulmonary disease (see comment below). The first systematic review (search date 1999; 23 double blind RCTs; 3 RCTs in people with chronic obstructive pulmonary disease; 20 RCTs in people with chronic bronchitis not defined further; > 6000 people) found that mucolytics for 3–6 months significantly reduced the average number of exacerbations and days of disability compared with placebo (exacerbations, WMD: -0.066 exacerbations/month, 95% CI -0.077 exacerbations/month to -0.054 exacerbations/month; days of disability, WMD: -0.56 days/month, 95% CI -0.77 days/months to -0.35 days/month).⁶³ The second systematic review (search date 1995; 9 RCTs, 7 of which were included in the first review⁶³) compared N-acetylcysteine versus placebo for 3–24 months.⁶⁴ It found that N-acetylcysteine reduced exacerbations compared with placebo (overall weighted effect size: 1.37, 95% CI 1.25 to 1.50; reduction 235). The first subsequent RCT found no significant difference in exacerbations between ambroxol 75 mg twice daily and placebo at 1 year (242 people with chronic obstructive pulmonary disease (COPD); percentage free from exacerbations 56% with ambroxol v 53% with placebo; $P = 0.36$).⁶⁵ The second subsequent RCT found no significant difference in forced expiratory volume in 1 second[Ⓞ] decline and exacerbations between N-acetylcysteine 600 mg daily and placebo at 3 years (difference in yearly decline in forced expiratory volume in 1 second: 8 mL, 95% CI -25 mL to $+10$ mL; exacerbations per year: 1.25 with acetylcysteine v 1.29 with placebo; HR 0.99, 95% CI 0.89 to 1.10). Prespecified subgroup analysis was performed for people with moderate or severe COPD, and people who did or did not use inhaled corticosteroids at entry. It found that 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). It found no significant difference in any of the other subgroup comparisons.⁶⁶

Harms: The first systematic review found no significant difference between mucolytics and placebo in the total number of adverse events.⁶³ In the earlier studies, the adverse effects of N-acetylcysteine were mainly mild gastrointestinal complaints. The first subsequent RCT found similar rates of adverse events with ambroxol and placebo (data not reported).⁶⁵ The second subsequent RCT found no drug related adverse events (data not reported).⁶⁶

Comment: The results of the reviews should be interpreted with caution.^{63,64} It was unclear how many people included in the reviews had COPD. In both reviews, there was significant heterogeneity among the RCTs, and symptom scores could not be pooled.^{63,64} The second subsequent RCT suggested that N-acetylcysteine may improve exacerbations in people not already taking inhaled corticosteroids.⁶⁶ However, the relative effects of these treatments cannot be determined based on the current evidence, so a direct comparison is required.

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OPTION PROPHYLACTIC ANTIBIOTICS

One systematic review found limited evidence of a small reduction in exacerbation rates and days with disability with prophylactic antibiotics. These benefits probably do not outweigh the harms of antibiotics, especially the development of antibiotic resistance. All of the identified RCTs were conducted more than 30 years ago, and the results are unlikely to apply to current practice.

Benefits: **Short term treatment:** We found no systematic review or RCTs. **Long term treatment:** We found one systematic review (search date not reported; 9 RCTs; 1055 people; see comment below) of prophylactic antibiotics (tetracycline, penicillin, trimethoprim, sulphadimidine, and sulphaphenazole) in people with chronic obstructive pulmonary disease or chronic bronchitis.⁶⁷ All trials were performed before 1970. The duration of the RCTs ranged from 3 months to 5 years. It found that antibiotics significantly reduced the risk of any exacerbation during the study compared with placebo (RR 0.91, 95% CI 0.84 to 0.99). It found that antibiotics slightly reduced the number of exacerbations per person per year but the reduction was not significant (WMD: -0.15, 95% CI -0.34 to + 0.04). It found that antibiotics significantly reduced the number of days of disability per person per month treated (WMD -0.95, 95% CI -1.89 to -0.01; 22% reduction).

Harms: In general, there was a poor reporting of possible adverse effects in most trials. Nevertheless, the review found that antibiotics slightly increased adverse effects compared with placebo (number of adverse effects; WMD per person per year treated: 0.01, 95% CI 0 to 0.02).⁶⁷

Comment: The results of this review should be interpreted with caution.⁶⁷ It was unclear from the descriptions of the original studies how many participants had chronic obstructive pulmonary disease (rather than chronic bronchitis without obstruction). Additionally, the data in the review are over 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 DOMICILIARY OXYGEN TREATMENT (LONG TERM)

One RCT in people with severe daytime hypoxaemia found that domiciliary oxygen improved survival compared with no domiciliary oxygen. A second RCT in people with severe hypoxaemia found that continuous oxygen reduced mortality compared with nocturnal oxygen. Three RCTs in people with milder hypoxaemia or with nocturnal hypoxaemia only, found no significant difference in mortality between long term domiciliary oxygen and no oxygen.

Benefits: **Long term treatment:** We found one systematic review (search date 2000, 5 RCTs).⁶⁸ The review could not perform a meta-analysis because of differences in trial design and participant selection. The first RCT (87 people), which compared daily oxygen supplementation for at least 15 hours versus no oxygen supplementation in people with severe daytime hypoxaemia (arterial oxygen tension [PaO₂] 5.3–8.0 kPa), found that domiciliary oxygen significantly reduced mortality over 5 years.⁶⁹ The second RCT (38 people with arterial desaturation at night) comparing nocturnal domiciliary oxygen versus room air found no significant difference in mortality at 3 years (figures not reported).⁷⁰ The third RCT (135 people with moderate hypoxaemia [PaO₂ 7.4–8.7 kPa]) comparing oxygen with no oxygen found no significant difference in survival at 3 years (HR 0.92, 95% CI 0.57 to 1.47; results presented graphically).⁷¹ The fourth RCT (203 people; PaO₂ < 7.4 kPa) compared continuous with nocturnal domiciliary oxygen treatment. Continuous oxygen was associated with a significant reduction in mortality over 24 months (22% with continuous oxygen v 41% with nocturnal oxygen; OR 0.45, 95% CI 0.25 to 0.81).⁷² The fifth RCT (76 people with moderate daytime hypoxaemia [PaO₂ 7.4–9.2 kPa] and significant nocturnal desaturation) comparing 2 years of nocturnal oxygen treatment versus placebo found no significant difference in survival.⁷³

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Harms: The systematic review gave no information on adverse effects.⁶⁸

Comment: Only one of the RCTs identified by the review was double blinded.⁶⁸ Domiciliary oxygen treatment seems to be more effective in people with severe hypoxaemia ($\text{PaO}_2 < 8.0 \text{ kPa}$) than in people with moderate hypoxaemia or those who have arterial desaturation only at night.

OPTION ALPHA₁ ANTITRYPSIN

One RCT in people with alpha₁ antitrypsin deficiency and moderate emphysema found no significant difference between alpha₁ antitrypsin infusion and placebo in the decline in forced expiratory volume in 1 second after 1 year.

Benefits: We found no systematic review. **Short term treatment:** We found no RCTs. **Long term treatment:** We found one RCT (56 people with alpha₁ antitrypsin deficiency and moderate emphysema, forced expiratory volume in 1 second[Ⓞ] (FEV₁) 30–80% predicted) comparing alpha₁ antitrypsin infusions 250 mg/kg versus placebo infusion (albumin) given monthly for at least 3 years. It found no significant difference in the decline in FEV₁ after 1 year (decline in FEV₁: 79 mL with alpha₁ antitrypsin v 59 mL with placebo, CI not reported; P = 0.25).⁷⁴

Harms: The RCT reported no adverse effects in people taking alpha₁ antitrypsin or placebo.⁷⁴

Comment: We found no clear evidence from observational studies on the effect of alpha₁ antitrypsin. For example, one cohort study (1048 people either homozygous for alpha₁ antitrypsin deficiency or with an alpha₁ antitrypsin concentration $\leq 11 \mu\text{mol/L}$, with mean FEV₁ $49 \pm 30\%$ predicted) compared weekly infusions of alpha₁ antitrypsin 60 mg/kg versus placebo for 3.5–7.0 years.⁷⁵ It found that alpha₁ 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 FEV₁, but in a subgroup of people with a mean FEV₁ of 35–49% predicted, alpha₁ antitrypsin significantly reduced the decline in FEV₁ (mean difference in FEV₁: 27 mL/year, 95% CI 3 mL/year to 51 mL/year, P = 0.03). A second cohort study (295 people homozygous for alpha₁ antitrypsin deficiency with FEV₁ < 65% predicted) compared 198 people who received weekly infusions of alpha₁ antitrypsin 60 mg/kg (duration not reported) versus 97 people who had never received alpha₁ antitrypsin. It found that alpha₁ antitrypsin significantly reduced the decline in FEV₁ (50 mL/year with alpha₁ antitrypsin v 80 mL/year with no alpha₁ antitrypsin, CI not reported; P = 0.02).⁷⁶

QUESTION What are the effects of non-drug interventions in stable chronic obstructive pulmonary disease?

OPTION PSYCHOSOCIAL INTERVENTIONS ALONE FOR SMOKING CESSATION

We found no systematic review or RCTs of psychosocial interventions alone for smoking cessation in people with chronic obstructive pulmonary disease.

Benefits: We found no systematic review or RCTs examining the effects of psychosocial interventions such as professional advice or counselling alone on the outcomes of interest in this review (forced expiratory volume in 1 second, peak expiratory flow[Ⓞ], exacerbations, dyspnoea score, quality of life, or survival), specifically in people with chronic obstructive pulmonary disease (see comment below). The review⁷⁷ identified two RCTs, both of which examined psychosocial interventions plus pharmacological interventions (see benefits of psychosocial plus pharmacological interventions, p 17).^{10,78}

Harms: We found no RCTs.

Comment: Despite the extensive literature on smoking cessation, we did not identify useful studies of psychosocial interventions alone because most studies focused on combinations of interventions; continuous abstinence or point prevalence rates of smoking cessation as single outcome measures; healthy people or mixed populations of healthy people and people with disease.

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OPTION PHARMACOLOGICAL INTERVENTIONS ALONE FOR SMOKING CESSATION

One systematic review found no RCTs of pharmacological interventions alone for smoking cessation in people with chronic obstructive pulmonary disease.

Benefits: We found one systematic review (search date 2002).⁷⁷ It found no RCTs examining the effects of pharmacological smoking cessation interventions alone for the outcomes of interest in this review (forced expiratory volume in 1 second), peak expiratory flow $\text{\textcircled{G}}$, exacerbations, dyspnoea score, quality of life, or survival) specifically in people with chronic obstructive pulmonary disease (COPD). The review⁷⁷ identified two RCTs, both of which examined pharmacological interventions plus psychosocial interventions (see benefits of psychosocial plus pharmacological interventions, p 17).^{10,78}

Harms: We found no RCTs.

Comment: One systematic review (search date 2001, 157 studies) assessed the effectiveness of bupropion and nicotine replacement therapy for smoking cessation, but did not focus solely on people with COPD.^{79,80} 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 undertaken 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 to be 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

One large RCT in people with mild chronic obstructive pulmonary disease found that nicotine gum plus a psychosocial smoking cessation and abstinence maintenance programme (with or without ipratropium) slowed the decline of forced expiratory volume in 1 second, and reduced respiratory symptoms and lower respiratory illnesses, but increased weight gain compared with usual care (without psychosocial intervention). The RCT found no significant difference between treatments in all cause mortality at 5 years, but it found that smoking cessation reduced all cause mortality compared with usual care at 14.5 years.

Benefits: One systematic review (search date 2002)⁸¹ identified two RCTs examining psychosocial plus pharmacological interventions in people with chronic obstructive pulmonary disease (COPD).^{10,78} The first RCT (5887 smokers, age 35–60 years, with spirometric signs of early COPD, mean prebronchodilator forced expiratory volume in 1 second $\text{\textcircled{G}}$ [FEV₁] 2640 mL, mean of 30 cigarettes smoked per day) compared three treatments: smoking cessation intervention plus placebo; smoking cessation intervention plus ipratropium; and usual care.¹⁰ 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.⁸² The RCT 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

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with smoking cessation intervention v 5% at 5 years and 6% at 11 years with usual care; P value not reported).⁸³ It found that the smoking cessation intervention (with and without ipratropium) significantly improved FEV₁ compared with usual care after 1 and 5 years and that the smoking intervention plus ipratropium significantly improved FEV₁ compared with the smoking cessation intervention alone at 1 and 5 years (change in FEV₁ at 1 year: -34.3 mL with usual care v +11.2 mL with smoking cessation intervention v +38.8 mL with intervention plus ipratropium; P < 0.005 for each between treatment comparison; at 5 years, completer analysis [around 90% of participants]: -267 mL with usual care v -208 mL with smoking cessation intervention v -184 mL with intervention plus ipratropium; P ≤ 0.002 for all comparisons).¹⁰ In further analyses, both treatments using a smoking cessation intervention were combined. After 11 years, smoking intervention reduced the decline in FEV₁ compared with usual care (change from baseline: -502 mL with intervention v +587 mL with usual care; P = 0.001).⁸⁴ 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).⁸⁵ The smoking cessation intervention significantly reduced cough, phlegm, wheezing, and dyspnoea compared with usual care at 5 years (by intention to treat analysis, cough for ≥ 3 months/year: 15% with intervention v 23% with usual care; phlegm for ≥ 3 months/year: 12% with intervention v 20% with usual care; presence of wheezing: 25% with intervention v 31% with usual care; presence of dyspnoea: 19% with intervention v 24% with usual care, all P < 0.0001).⁸⁶ There was no significant difference between the three treatments in all cause mortality at 5 years (2.60% with usual care v 2.24% with smoking cessation intervention v 2.75% with intervention plus ipratropium; P = 0.58).⁸⁷ Smoking cessation intervention (with and without ipratropium) significantly reduced all cause mortality compared with usual care at 14.5 years (8.83 per 1000 person-years with smoking cessation intervention v 10.83 per 1000 person-years with placebo; HR for mortality 1.18, 95% CI 1.02 to 1.37).⁸⁸ The second RCT (404 people with mild or moderate COPD, smoking an average of 28 cigarettes per day, mean age 54 years) compared bupropion plus counselling versus placebo plus counselling for 12 weeks with 6 months' follow up, but only reported abstinence rates and adverse effects.⁷⁸ This study did not provide data about the effects on FEV₁ changes, peak expiratory flow, exacerbations, dyspnoea score, quality of life, or survival. It found that bupropion (slow release 150 mg twice daily) 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; see comment below).⁷⁸

Harms:

In the first RCT,¹⁰ 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 (5.10% for men and 3.95% for women); mouth irritation (6.2% for men and 6.5% for women); mouth ulcers (4.4% for men and 5.3% for women); nausea (1.8% for men and 3.8% for women); and hiccups (2.8% for men and 3.8% for women).⁸⁹ The smoking intervention increased weight at 1 and 5 years in both men and women compared with usual care, but the significance was not reported (weight gain, 1 year: 2.61 kg with intervention v 0.61 kg with usual care for men and 2.63 kg v 1.10 kg for women; 5 years: 3.9 kg with intervention v 2.60 kg with usual care for men and 4.75 kg v 2.84 kg for women).⁹⁰ The second RCT found similar rates of discontinuation because of adverse effects between treatment groups (6% with placebo v 7% with bupropion). It found higher rates of serious adverse effects with placebo (2.5% with placebo v 0.5% with bupropion).⁷⁸

Comment: None.

OPTION

PULMONARY REHABILITATION

New

Two systematic reviews found that multi-modality pulmonary rehabilitation improved quality of life, maximal exercise capacity, and functional exercise capacity.

Benefits:

We found two systematic reviews investigating pulmonary rehabilitation.^{91,92} The first systematic review (search date 2000, 23 RCTs) found that pulmonary rehabilitation significantly improved dyspnoea, fatigue, emotional function, and mastery compared

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with usual care (Chronic Respiratory Disease Questionnaire: dyspnoea: 9 RCTs; 519 people; WMD 1.0, 95% CI 0.8 to 1.2; fatigue: 8 RCTs; 513 people; WMD 0.9, 95% CI 0.7 to 1.1; emotional function: 8 RCTs; 513 people; WMD 0.7, 95% CI 0.4 to 1.0; mastery: 8 RCTs; 513 people; WMD 0.9, 95% CI 0.7 to 1.2). In the domains of dyspnoea, fatigue, and mastery, the effect was larger than the minimally clinically important difference of 0.5 units. It found that pulmonary rehabilitation improved maximal exercise capacity and functional exercise capacity compared with usual care (incremental cycle ergometer test: 14 RCTs; 488 people; WMD 5.46 watts, 95% CI 0.49 watts to 10.23 watts; 6 minute walk test: 10 RCTs; 454 people; WMD 49 m, 95% CI 26 m to 72 m). The confidence interval for functional exercise capacity is outside the minimal clinically significant difference of between 37 m and 71 m for the 6 minute walk test. There is no generally accepted minimal clinically important difference for the cycle ergometer test. The second systematic review (search date 2000; 20 RCTs, 12 of which were also included in the first systematic review)⁹² found that pulmonary rehabilitation significantly improved exercise capacity and shortness of breath compared with control (walking test: 20 RCTs; 979 people with symptomatic chronic obstructive pulmonary disease or impaired exercise capacity; standard effect size 0.71, 95% CI 0.43 to 0.99; Chronic Respiratory Disease Questionnaire – shortness of breath: 12 RCTs; 723 people; standard effect size 0.62, 95% CI 0.26 to 0.91).

Harms: The systematic review found no adverse effects with pulmonary rehabilitation.

Comment: There are indications that the effects of pulmonary rehabilitation without reinforcement do not last longer than 1 year.

OPTION

INSPIRATORY MUSCLE TRAINING (ALONE)

New

One systematic review found that inspiratory muscle training improved inspiratory muscle strength and endurance, and dyspnoea at rest and during exercise compared with control, but it found no significant difference in exercise capacity between groups. The review found that adding inspiratory muscle training to general exercise reconditioning improved inspiratory muscle strength and endurance, but did not have any additional beneficial effects on exercise capacity.

Benefits: We found one systematic review (search date 2000).⁹³ **Inspiratory muscles training versus control:** The review found that inspiratory muscle training (with or without general exercise rehabilitation) significantly improved inspiratory muscle strength, endurance, and dyspnoea compared with control (inspiratory muscle strength: 15 RCTs; 383 people; WMD 0.56 cm H₂O, 95% CI 0.35 cm H₂O to 0.77 cm H₂O; inspiratory muscle endurance: 7 RCTs; number of people not reported; WMD 0.41 seconds, 95% CI 0.14 seconds to 0.68 seconds; Borg exercise related dyspnoea: 5 RCTs; number of people not reported; weighted average effect size –0.55, 95% CI –0.90 to +0.19; Transitional Dyspnoea Index: 2 RCTs; number of people not reported; weighted average effect size 2.3, 95% CI 1.44 to 3.15). It found no significant difference in inspiratory muscle endurance (maximal voluntary ventilation), laboratory exercise capacity, and functional exercise capacity between groups (endurance: 4 RCTs; number of people not reported; WMD 0.21 L/minute, 95% CI –0.29 L/minute to +0.70 L/minute; laboratory exercise capacity VO₂max: 5 RCTs; number of people not reported; WMD +0.04 L/minute, 95% CI –0.36 L/minute to +0.29 L/minute; laboratory exercise capacity VEmax: 5 RCTs; number of people not reported; WMD +0.03 L/minute, 95% CI –0.03 L/minute to +0.35 L/minute; functional exercise capacity 6 or 12 minute walking distance: 8 RCTs; number of people not reported; WMD +0.22 m, 95% CI –0.05 m to +0.48 m).⁹³ **Inspiratory muscle training plus general exercise reconditioning versus general exercise reconditioning alone:** The review found that inspiratory muscle training plus general exercise reconditioning improved inspiratory muscle strength and inspiratory muscle endurance compared with general exercise reconditioning alone (inspiratory muscle strength: 6 RCTs; number of people not reported; WMD 0.47 cm H₂O, 95% CI 0.15 cm H₂O to 0.79 cm H₂O; inspiratory muscle endurance: 3 RCTs; number of people not reported; WMD 0.55 seconds, 95% CI 0.14 seconds to 0.97 seconds). Combination therapy significantly improved muscle strength in people with inspiratory muscle weakness, but not in those without (with weakness: 3 RCTs;

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number of people not reported; WMD + 16 cm H₂O; P < 0.001; without weakness: 3 RCTs; number of people not reported; WMD -3 cm H₂O; P = 0.54). It found no significant difference in functional exercise capacity between groups (6 or 12 minute walk test: 4 RCTs; number of people not reported; WMD + 0.20 m, 95% CI -0.21 m to + 0.61 m).

Harms: The systematic review did not report harms.⁹³

Comment: None.

OPTION

PERIPHERAL MUSCLE STRENGTH TRAINING (ALONE)

New

One systematic review found that peripheral muscle training improved upper body and leg strength compared with no treatment or other exercise training. It found that pulmonary function, maximal exercise capacity, walking endurance, cycling endurance, and psychological wellbeing were similar in both groups.

Benefits: We found one systematic review (search date not reported),⁹⁴ which found that resistance training improved upper body and knee extensor strength compared with no treatment or other exercise training (upper body strength: 3 RCTs; 136 people; effect size 0.70, 95% CI 0.28 to 1.11; knee extensor strength: 5 RCTs; 202 people; effect size 0.90, 95% CI 0.42 to 1.38). The review did not present a meta-analysis of pulmonary function, maximal exercise capacity, and walking endurance. These outcomes were generally similar with resistance training and no treatment or other exercise training (pulmonary function: 1 RCT; 14 people; forced expiratory volume in 1 second (FEV₁) effect size -0.22, 95% CI -0.79 to + 0.34; forced vital capacity effect size -0.24, 95% CI -0.80 to + 0.33; 1 RCT; 48 people; maximal inspiratory pressure effect size -0.40, 95% CI -0.67 to -0.13; maximal expiratory pressure effect size -0.47, 95% CI -0.74 to -0.20; 1 RCT; 62 people; maximal inspiratory pressure effect size 0.57, 95% CI 0.44 to 0.71; maximal exercise capacity: 1 RCT; 45 people; maximal oxygen consumption (VO₂) effect size 0.57, 95% CI 0.34 to 0.80; minute ventilation (VE) effect size 0.49, 95% CI 0.26 to 0.72; 1 RCT; 95 people; VO₂ effect size 0, 95% CI -0.19 to + 0.19; VE effect size 0.56, 95% CI 0.36 to 0.76; 1 RCT; 72 people; VO₂ effect size -0.11, 95% CI -0.35 to + 0.13; VE effect size 0.05, 95% CI -0.19 to + 0.28; 1 RCT; 34 people; VO₂ effect size -1.10, 95% CI -1.42 to -0.78; bike effect size 0.36, 95% CI 0.08 to 0.65; 1 RCT; 48 people; VO₂ effect size 0.08, 95% CI -0.18 to + 0.34; bike effect size 0.07, 95% CI -0.20 to + 0.33; 1 RCT; 62 people; VO₂ effect size 0.14, 95% CI 0.01 to 0.27; bike effect size 0.08, 95% CI -0.05 to + 0.21; walking endurance: 1 RCT; 45 people; 6 minute walk test effect size 0.76, 95% CI 0.52 to 1.00; 1 RCT; 50 people; 6 minute walk test effect size 1.49, 95% CI 1.08 to 1.90; 1 RCT; 14 people; 12 minute walk test effect size 0.14, 95% CI -0.41 to + 0.71; 1 RCT; 72 people; shuttle walk test effect size 0.28, 95% CI 0.04 to 0.52; 1 RCT; 48 people; 6 minute walk test effect size -0.06, 95% CI -0.33 to + 0.20; 1 RCT; 62 people; 6 minute walk test effect size 0.26, 95% CI 0.13 to 0.38). One RCT in the review found that peripheral muscle training improved cycling endurance compared with no treatment, and two RCTs in the review found that endurance training improved cycling endurance compared with peripheral muscle training (1 RCT; 34 people; effect size 4.42, 95% CI 3.46 to 5.38; 1 RCT; 72 people; effect size -1.09; 1 RCT; 48 people; -0.74). One RCT in the review found that peripheral muscle training improved psychological wellbeing compared with before treatment, although four RCTs in the review found similar psychological wellbeing with peripheral muscle treatment and no treatment or other exercise training (36 item short form questionnaire: 1 RCT; 50 people; health perception effect size 0.22, 95% CI -0.19 to + 0.63; health role effect size 2.03, 95% CI 1.62 to 2.44; emotion effect size 1.39, 95% CI 0.99 to 1.80; mental effect size 1.36, 95% CI 0.95 to 1.77; energy effect size 2.08, 95% CI 1.67 to 2.49; chronic respiratory disease questionnaire: 1 RCT; 45 people; shortness of breath effect size -0.12, 95% CI -0.35 to + 0.10; emotion effect size 0, 95% CI -0.22 to + 0.22; fatigue effect size -0.26, 95% CI -0.49 to -0.04; mastery effect size -0.84, 95% CI -1.08 to -0.59; 1 RCT; 72 people; shortness of breath effect size -0.09, 95% CI -0.33 to + 0.15; emotion effect size + 0.19, 95% CI -0.04 to + 0.43; fatigue effect size -0.10, 95% CI -0.34 to + 0.14; mastery effect size 0, 95% CI -0.24 to + 0.24; 1 RCT; 48 people; total effect size 0, 95% CI -0.26 to + 0.26; 1 RCT; 62 people; total effect size 0.37, 95% CI 0.24 to 0.50).

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Harms: The review found that no studies reported adverse events or withdrawal because of adverse effects of peripheral muscle training.⁹⁴

Comment: None.

OPTION

GENERAL PHYSICAL ACTIVITY ENHANCEMENT (ALONE)

New

One systematic review found that general physical activity enhancement (walking, cycling, or swimming) improved exercise tolerance compared with control. It found no consistent evidence of a difference in quality of life and dyspnoea.

Benefits: 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).⁹⁵ The review did not present meta-analysis of outcomes. Three RCTs found that physical activity enhancement significantly improved exercise tolerance compared with control (1 RCT; 23 people; 6 minute walk distance: difference 5 m CI not reported; 1 RCT; 48 people; walking test: difference 5942 joules CI not reported; 1 RCT; 43 people; walking test: difference 3861 joules CI not reported; 1 RCT; 58 people; differences reported as significant), but one RCT found no difference (38 people; 6 minute walking test: difference 29 m CI not reported).⁹⁵ One RCT found that physical activity enhancement improved quality of life (1 RCT; 23 people; mean change in Chronic Respiratory Disease Questionnaire score: dyspnoea [range 5–35]: 6 with exercise v 0 with control; fatigue [range 4–28]: 5 with exercise v 0 with control; emotion [range 7–49]: 5 with exercise v 2 with control; mastery [range 4–28]: 4 with exercise v –1 with control; significance not reported for chronic obstructive pulmonary disease subgroup),⁹⁶ but one RCT found no significant difference (1 RCT; 38 people; mean change in the St George's Respiratory Questionnaire total score: –2.1 with exercise v –2.1 with control; difference 0.1, 95% CI –9.9 to +10.0).⁹⁷ One RCT found that physical activity enhancement improved dyspnoea (data reported above),⁹⁶ but one RCT found no significant difference (1 RCT; 38 people; mean change in Borg dyspnoea scale after walking test: 0.4 with exercise v 0.9 with control; difference –0.5, 95% CI –1.5 to +0.6).⁹⁷

Harms: The systematic review did not report on harms.⁹⁵

Comment: None.

OPTION

MAINTAINING HEALTHY WEIGHT

Two systematic reviews found no consistent evidence that nutritional supplementation improves lung function or exercise capacity in people with stable chronic obstructive pulmonary disease.

Benefits: **Nutritional supplementation versus placebo or usual diet:** We found two systematic reviews.^{98,99} The first systematic review found similar weight gain with nutritional supplementation and placebo or usual diet for at least 2 weeks (search date 2004; 10 RCTs; 337 people; SMD + 0.11, 95% CI –0.17 to + 0.40). It also found similar changes in arm muscle circumference, triceps skinfold thickness, 6 minute walk distance, forced expiratory volume in 1 second, maximal inspiratory pressure, and maximal expiratory pressure with nutritional supplementation and placebo or usual diet for at least 2 weeks (arm muscle circumference: 6 RCTs; 132 people; SMD 0.11, 95% CI –0.23 to + 0.45; triceps skinfold thickness: 5 RCTs; 97 people; SMD + 0.36, 95% CI –0.04 to + 0.76; 6 minute walk distance: 3 RCTs; 77 people; SMD 0.03, 95% CI –0.41 to + 0.47; forced expiratory volume in 1 second: 5 RCTs; 119 people; SMD + 0.03, 95% CI –0.33 to + 0.39; maximal inspiratory pressure: 4 RCTs; 70 people; SMD + 0.01, 95% CI –0.46 to + 0.48; maximal expiratory pressure: 4 RCTs; 70 people; SMD + 0.10, 95% CI –0.57 to + 0.37).⁹⁹ The second systematic review identified 21 RCTs, which were classified according to the type (different composition of carbohydrates/fat), duration of supplementation (one meal, < 2 weeks, > 2 weeks), and presence of anabolic substances.⁹⁸ 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

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systematic review described above. 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).

Harms: The two systematic reviews did not report any adverse effects.^{98,99}

Comment: The two systematic reviews are difficult to interpret because of heterogeneity between 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.¹⁰⁰ Other variations between the studies included: outcome variables; severity of chronic obstructive pulmonary disease 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 (FEV₁) The volume breathed out in the first second of forceful blowing into a spirometer, measured in litres

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

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