

Section 7.6.1 Inhaled corticosteroids

Literature search

N=134 Inhaled steroids
N=126 Combined – those papers that refer to oral and inhaled steroids
N=211 Excluded from abstracts
N=49 Full papers ordered and of these;
N=6 Papers critically appraised
N=43 Papers excluded
N=1 Paper found on cross referencing (excluded)
N=2 Cited by GDG members

Only trials of duration of 36 months or greater included.

(An exception to this was the Systematic Review by Alsaeedi 2002 which contained trials of a duration of 6 months but ranging as far as 40 months. Hence to be inclusive this systematic review as critically appraised and discussed).

Author	Publication Date	ID	SIGN Grade	Hierarchy
Alsaeedi, A., Sin, D. D., & McAlister, F. A. 2002, "The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: A systematic review of randomized placebo-controlled trials", <i>American Journal of Medicine</i> , vol. 113, no. 1, pp. 59-65. Ref ID: 1668	2002	1668	+	1a
Van Grunsven, P. M., Van Schayck, C. P., Derenne, J. P., Kerstjens, H. A. M., Renkema, T. E. J., Postma, D. S., Similowski, T., Akkermans, R. P., Pasker-De Jong, P. C. M., Dekhuijzen, P. N. R., Van Herwaarden, C. L. A., & Van Weel, C. 1999, "Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: A meta-analysis",	1999	879	+	1a

<i>Thorax</i> , vol. 54, no. 1, pp. 7-14.				
BURGE, P. S., Calverley, P. M. A., Jones, P. W., Spencer, S., Anderson, J. A., & Maslen, T. K. 2000, "Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial", <i>British Medical Journal</i> , vol. 320, no. 7245, pp. 1297-1303. Ref ID: 194	2000	194	+	1b
The Lung Health Study Research Group, Altose, M. D., Redline, S., Deitz, et al. 2000, "Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease", <i>New England Journal of Medicine</i> , vol. 343, no. 26, pp. 1902-1909. Ref ID: 193	2000	193	++	1b
Vestbo, J., Sorensen, T., Lange, P., Brix, A., Torre, P., & Viskum, K. 1999, "Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial", <i>Lancet</i> , vol. 353, no. 9167, pp. 1819-1823. Ref ID: 196	1999	196	+	1b
Pauwels, R. A., Lofdahl, C. G., Laitinen, L. A., Schouten, J. P., POSTMA, D. S., Pride, N. B., & Ohlsson, S. V. 1999, "Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking", <i>New England Journal of Medicine</i> , vol. 340, no. 25, pp. 1948-1953. Ref ID: 195	1992	195	++	1b

Pauwels, R. A., Lofdahl, C.-G., Pride, N. B., POSTMA, D. S., Laitinen, L. A., & Ohlsson, S. V. 1992, "European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): Hypothesis and design", <i>European Respiratory Journal</i> , vol. 5, no. 10, pp. 1254-1261. Ref ID: 1696	1992	1696		
Lofdahl, C. G., POSTMA, D. S., Laitinen, L. A., Ohlsson, S. V., Pauwels, R. A., & Pride, N. B. 1998, "The European respiratory society study on chronic obstructive pulmonary disease (EUROSCOP): Recruitment methods and strategies", <i>Respiratory Medicine</i> , vol. 92, no. 3, pp. 467-472. Ref ID: 1707	1998	1707		
Johnell, O., Pauwels, R., Lofdahl, C.-G., Laitinen, L. A., POSTMA, D. S., Pride, N. B., & Ohlsson, S. V. 2002, "Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler", <i>European Respiratory Journal</i> , vol. 19, no. 6, pp. 1058-1063. Ref ID: 1711	2002	1711	++	1b subgroup analysis of ID 195
Jones, P. W., Willitis, L. R., Burge, P. S., Calverley, P. M. A., on behalf of the inhaled steroids in obstructive lung disease in Europe study investigators. (2003). Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. <i>Eur Respir J</i> , 21, 68-73.	2003	1787	+	1b
Burge, P. S., Calverley, P. M. A., Jones, P. W., Spencer, S., Anderson, J. A., on behalf of the ISOLDE Study Group. (2003).	2003	1791	+	1b

Prednisolone response in patients with chronic obstructive pulmonary disease: Results from the ISOLDE study. Thorax, 58, 1-5				
Sin, D. D., Man, S. F. P. (2003). Inhaled corticosteroids and survival in chronic obstructive pulmonary disease: Does the dose matter? European Respiratory Journal, 21, 260-266.	2003	19360	-	III

Author / Title / Reference / Yr	Alsaeedi, A., Sin, D. D., & McAlister, F. A. 2002, "The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: A systematic review of randomized placebo-controlled trials", <i>American Journal of Medicine</i> , vol. 113, no. 1, pp. 59-65. Ref ID: 1668
N=	RCTs=9. N=3976. Durations=6 to 40 months.
Research Design	RCTs
Aim	To determine whether inhaled corticosteroids improve clinical outcomes for pts with stable COPD.
Operational Definition	Baseline FEV1 and exacerbation definitions given for each study in Table 1 extracted from the primary study paper.
Population	Stable COPD
Intervention	Inhaled corticosteroids given for at least 6 months
Comparison	Placebo controlled
Outcome	Exacerbations / adverse effects / all-cause mortality
Characteristics	As per Table 1 attachment
Results	<p>Exacerbation rate Use of inhaled corticosteroid therapy reduced the rate of exacerbations (RR=0.70; 95% CI: 0.58 to 0.84). There were similar benefits in those who were or were not pre-treated with systemic steroids.</p> <p>The test for heterogeneity was significant (p=0.03) indicating that the effects of corticosteroids on exacerbations varied among the studies. Possibly due to discrepant results of the Vestbo et al 1999 study (RR 0.96; 95% CI: 0.77 to 1.20). The authors cite the most likely explanation for the disparity as the definition of COPD exacerbation adopted by the investigators "the less rigorous definition may have led to misclassification of clinical outcomes". In an analysis that excluded the Vestbo study the summary estimate for the efficacy of inhaled corticosteroids in preventing COPD exacerbations was RR 0.67 (95% CI: 0.63 to 0.71) with no evidence of heterogeneity.</p>

	<p>A sensitivity analysis was undertaken to examine differences in treatment efficacy by dosage of intervention. No dose response effect was demonstrated.</p> <p>All cause mortality Non significant</p> <p>Adverse Events Inhaled corticosteroid therapy was associated with: Increased rates of oropharyngeal candidiasis (RR=2.1; 95%CI 1.5 to 3.1) Increased rates of skin bruising (RR=2.1; 95% CI 1.6 to 2.8) Bone mineral density – variable between studies Cortisol concentrations – variable between studies (abstract states “lower mean cortisol levels”) Cataract – No difference in rates Fracture – No difference in rates</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
Papers included	<p>Studies with systemic steroid run in phase: Vestbo et al 1999, Senderovitz et al 1999, Bourbeau et al 1998, Burge et al 2000.</p> <p>Studies without systemic steroid run in phase: Lung Health Study 2000, Renkema et al 1996, Pauwels et al 1999, Weir et al 1999, Paggiaro et al 1998.</p>
NCC CC ID	1668

Author / Title / Reference / Yr	Van Grunsven, P. M., Van Schayck, C. P., Derenne, J. P., Kerstjens, H. A. M., Renkema, T. E. J., Postma, D. S., Similowski, T., Akkermans, R. P., Pasker-De Jong, P. C. M., Dekhuijzen, P. N. R., Van Herwaarden, C. L. A., & Van Weel, C. 1999, "Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: A meta-analysis", <i>Thorax</i> , vol. 54, no. 1, pp. 7-14.
N=	<p>N=3 studies (N =303). Patients included in the meta analysis =183.</p> <p>Location: Not reported</p> <p>Duration: 24 months (only RCTs of >24 months duration included)</p>
Research Design	Meta analysis
Aim	Are inhaled corticosteroids able to slow down the decline in lung function (FEV1) in COPD?
Operational Definition	<p>Patients with a strict diagnosis of COPD (chronic breathlessness especially on exertion and / or (productive) cough during 3 or more months per year in two successive years), aged 40 or over, previous or current non-smokers, FEV1 following treatment with beta-2 agonist less than or equal to FEV1 predicted –1.64SD, bronchodilator response to beta-2 agonist less than or equal to 9% of FEV1 predicted.</p> <p>People with alpha-1-antitrypsin deficiency or a history of asthma were excluded.</p>

	The definition of exacerbation varied between the three studies.
Population	Moderately severe COPD
Intervention	N=95 Inhaled corticosteroids: 800µg beclomethasone, 1500µg beclomethasone or 1600µg budesonide.
Comparison	N=88 Placebo
Outcome	The primary outcome was prebronchodilator decline in FEV1 measured at two monthly or three monthly intervals. All measurements were made in a stable state in the absence of an exacerbation. Secondary outcomes were postbronchodilator decline in FEV1, number of dropouts and number of exacerbations (defined as doctor's diagnosis of increasing respiratory symptoms requiring a short course of systemic corticosteroids and or antibiotics).
Characteristics	Average age 61yrs FEV1 – treatment group 1.42, placebo group 1.30 FEV (% pred) – treatment group 46, placebo group 44
Results	<p>Effect of inhaled corticosteroids on FEV1 (repeated measurement analysis): Prebronchodilator FEV1 versus placebo, after adjustment of variables with $p \leq 0.05 = +0.034$ 1/year (95%CI: 0.005 to 0.063, $p=0.026$). Low dose estimate = $+0.0021$ 1/year (95%CI: -0.061 to 0.065), high dose estimate = $+0.039$ 1/year (95%CI: 0.008 to 0.070, $p=0.043$). Postbronchodilator FEV1 effect = $+0.039$ 1/year (95%CI: 0.006 to 0.084, $p=0.095$) overall, maintained in high dose but not low dose groups when dose was taken into account.</p> <p>Determinants of lung function slope and corticosteroid response: The use of short acting beta-2-agonists and a higher baseline FEV1 had an independent effect. No interaction of any of the variables analysed with the inhaled corticosteroid treatment was observed.</p> <p>Effect on exacerbations and dropouts: No beneficial effect was observed on the exacerbation rate. The drop out rate was 32% in the placebo group and 36% in the inhaled corticosteroid group. Worsening of disease was the reason for drop out in four of the patients in the treatment group compared to nine in the placebo group.</p> <p>Adverse effects: In the inhaled steroid group 17/95 people dropped out due to adverse effects compared to 12/88 in the placebo group (chi-square= 0.62, $p=0.43$). No serious adverse effects relating to the treatment occurred.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
Comments	<ul style="list-style-type: none"> The Derenne study was only published in abstract form however >80% of the patients in the meta analysis were from this study. The duration of the study by Kerstjens et al was 30 months, only patient data up to 24 months of study were used.
Papers included	Renkema 1996 (N=58), Derenne 1995 (N=194) and Kerstjens 1992 (N=51).
NCC CC ID	879

Author / Title / Reference / Yr	BURGE, P. S., Calverley, P. M. A., Jones, P. W., Spencer, S., Anderson, J. A., & Maslen, T. K. 2000, "Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial", <i>British Medical Journal</i> , vol. 320, no. 7245, pp. 1297-1303. Ref ID: 194
N=	N=751. Location=UK. Sites=18 hospitals. Duration=36 months.
Research Design	Randomised, double-blind placebo-controlled study
Aim	To determine the effect of long term inhaled corticosteroids on lung function, exacerbations, and health status in patients with moderate to severe chronic obstructive pulmonary disease.
Operational Definition	Baseline FEV1 after bronchodilator was at least 0.8 litres but <85% of predicted normal, and the ratio of FEV1 to FVC <70%. Exacerbation was defined as worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics, or both. Specific symptom criteria were not used.
Population	Moderate to severe COPD (non asthmatic)
Intervention	N=376 Inhaled fluticasone propionate 500ug twice daily from a metered dose inhaler
Comparison	N=375 Identical placebo
Outcome	Rate of decline in FEV1 after the bronchodilator / health status / frequency of exacerbations / respiratory withdrawals / safety measures / morning serum cortisol concentration, incidence of adverse events.
Characteristics	<p>Previous use of inhaled and oral corticosteroids was permitted</p> <p>Excluded if FEV1 response to 400ug salbutamol exceeded 10% of predicted normal</p> <p>Nasal and ophthalmic corticosteroids, theophyllines, and all other bronchodilators were allowed during the study. Throughout the trial pts used salbutamol 100ug/puff or ipratropium bromide 40ug/puff or both for symptomatic relief.</p> <p>Aged 40 to 75 years. Mean age 64yrs.</p> <p>Gender: Placebo=97 women / Fluticasone N=94 women</p> <p>Previous use of regular inhaled corticosteroids: Placebo N=214 / Fluticasone N=192</p>
Results	<p><i>FEV1</i></p> <p>There was no significant difference in the annual rate of decline in FEV1. FEV1 59ml/yr in the placebo group and 50ml/yr in the fluticasone propionate group.</p> <p>The predicted mean FEV1 at 3 and 36 months in the fluticasone propionate group was 76ml and 100ml higher, respectively, than in the placebo group (p<0.001).</p> <p>Mean FEV1 after bronchodilator remained significantly higher throughout the study with fluticasone propionate compared with placebo (p<0.001).</p> <p><i>"There was no significant relation between FEV1 response to oral corticosteroid or fluticasone propionate (p=0.056)".</i></p> <p><i>Exacerbation rate</i></p>

	<p>There was a reduction of 25% from 1.32 a year on placebo to 0.99 a year on fluticasone propionate (p=0.026).</p> <p><i>Health status</i></p> <p>The total respiratory questionnaire score was not significantly different between treatment groups over the first 6 months of treatment.</p> <p>The respiratory questionnaire score deteriorated at a faster rate by 3.2 units/yr on placebo and 2.0 units/yr on fluticasone propionate (p=0.0043).</p> <p><i>Withdrawals</i></p> <p>Withdrawals due to respiratory disease not related to malignancy were higher in the placebo group, 25% vs 19%, p=0.034.</p> <p><i>Safety</i></p> <p>There was a significant (p<0.032) decrease in mean cortisol concentrations with fluticasone propionate compared with placebo. 5% of patients on fluticasone propionate had values below the normal range during the study. No decreases were associated with any signs or symptoms of hypoadrenalism</p> <p>Bruising N=15 in placebo group / N=27 in fluticasone group</p> <p>Fractures N=17 in placebo group / N=9 in fluticasone group</p> <p><i>Conclusion</i></p> <p>In pts with moderate to severe disease, fluticasone propionate 1 mg daily resulted in fewer exacerbations, a reduced rate of decline in health status, and higher FEV1 values than placebo treatment BUT this relates to fluticasone propionate 500ug twice daily via a MDI for three years in moderate to severe COPD. There was no change in the primary end point of decline in FEV1.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	194

Author / Title / Reference / Yr	The Lung Health Study Research Group, Altose, M. D., Redline, S., Deitz, et al. 2000, "Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease", <i>New England Journal of Medicine</i> , vol. 343, no. 26, pp. 1902-1909. Ref ID: 193
N=	N=116. Sites= 10 centre. Duration=Mean duration of follow up was 40 months
Research Design	Placebo controlled, double blind, randomised trial.
Aim	To ascertain whether anti-inflammatory therapy with inhaled corticosteroids would slow the decline in lung function.
Operational Definition	FEV1 to FVC less than 0.70 FEV1 that was 30 to 90% predicted.
Population	COPD

	Did not exclude asthma. % of participants with asthma 9.7 in the treatment group and 9.2 in the placebo group. Asthmatic responses not analysed separately in results. However, excluded those who regularly used bronchodilators or corticosteroids.
Intervention	Inhaled triamcinolone acetonide 600ug twice daily via MDI. (100 ug per inhalation) For each group, six inhalations twice daily were prescribed resulting in a dose of 1200ug per day for the triamcinolone group.
Comparison	Placebo (identical inhalers)
Outcome	Primary outcome: Rate of decline in FEV1 after administration of a bronchodilator. Secondary outcome: Respiratory symptoms, use of health care services, and airway reactivity. Subgroup analysis: In a sub study of N=412 bone density measured in lumbar spine and femur at baseline and one and three years.
Characteristics	Participants were recruited from among those who had previously participated in or been screened for the Lung Health Study (Anthonisen et al 1994 and Buist et al 1993). Aged between 40 to 69 years. Mean age 56 years. Excluded if used bronchodilators or oral or inhaled corticosteroids in the previous year. Mild to moderate abnormalities of pulmonary function, with an FEV1 before bronchodilator use of 64.1 +/- 13.3 % of predicted value.
Results	<p>FEV1 rate of decline No significant differences on the decline in the FEV1 or the FVC either before or after bronchodilator use. N=559 triamcinolone group. N=557 placebo group. Mean 44.2 +/- 2.9 vs 47.0 +/- 3.0 ml per year, p=0.50</p> <p>Respiratory symptoms “The incidence of respiratory symptoms over the preceding 12 months measured by the ATS Division of Lung Diseases questionnaire at the 36 month visit, did not differ significantly between the treatment groups with the exception of dyspnoea, which was more frequent in the placebo group (p=0.02)”.</p> <p>In relation to the number of new or increased respiratory symptoms categorised as moderate or severe per 100 per-years, the triamcinolone group had significantly fewer respiratory symptoms, 21.1 per 100 person-years vs 28.2 per 100 person-years, p=0.005</p> <p>Visits to physician The triamcinolone group had significantly fewer visits to a physician because of a respiratory illness, 1.2 per 100 person-years vs 2.1 per 100 person-years, p=0.03 There were no significant differences between the groups in the rate of visits to an emergency department (not resulting in hospitalisation) for either respiratory or non-respiratory conditions.</p> <p>Mortality There was no significant difference between the treatment groups in overall mortality.</p> <p>Airway reactivity The triamcinolone group had a lower airway reactivity in response to methacholine challenge at 9 and 33 months, p=0.02 for both comparisons.</p>

	<p>Subgroup analysis</p> <p>Bone density After three years, bone density of the lumbar spine (p=0.007) and the femur (p<0.001) was significantly lower in the triamcinolone group.</p> <p>Conclusion “Inhaled triamcinolone does not slow the rate of decline in lung function in people with COPD, but it improves airway reactivity and respiratory symptoms and decreases the use of health care services for respiratory problems. These benefits should be weighted against the potential long-term adverse effects of triamcinolone on bone mineral density”.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	193

Author / Title / Reference / Yr	Vestbo, J., Sorensen, T., Lange, P., Brix, A., Torre, P., & Viskum, K. 1999, "Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial", <i>Lancet</i> , vol. 353, no. 9167, pp. 1819-1823. Ref ID: 196
N=	N=290. Geographical location= Sites=Single centre nested in a continuing epidemiological survey (The Copenhagen City Heart Study). Duration=3 yr
Research Design	Parallel group, double blind RCT
Aim	To investigate the efficacy of inhaled budesonide on decline in lung function and respiratory symptoms
Operational Definition	ATS criteria for FEV1, vital capacity and FVC. Exacerbation defined as “an affirmative answer to the question, “Have you since your last visit experienced more cough and phlegm than usual?”.”
Population	Patients with COPD
Intervention	N=145 Inhaled budesonide 800ug in the morning and 400ug in the evening for 6/12 and then 400ug twice daily for 30 months.
Comparison	N=145 Placebo for 36 months
Outcome	Rate of FEV1 decline
Characteristics	Mean age 59yrs Mean FEV1 was 2.37 or 86% of predicted Gender 60% male

	<p>Study Inclusion Ratio of FEV1 and vital capacity of 0.7 or less FEV1 which showed no response (<15% change) to 1mg inhaled Terbutaline or prednisolone 37.5mg orally once daily for 10 days Oral, inhaled or parenteral steroids could be used during exacerbations for up to three periods of 4wks each year. Beta2 agonists, theophylline, disodium chromoglycate and mucolytics were allowed.</p> <p>Study Exclusion Asthma Continuous use of inhaled corticosteroids Concomitant use of beta-blockers was not allowed during the study.</p>
Results	<p>FEV1 decline No significant effect of budesonide was found on the rate of FEV1 decline.</p> <p>Exacerbations No statistically significant differences between the two groups were observed</p> <p>Symptoms No statistically significant differences between the two groups were observed</p> <p>Mortality There were nine deaths (four in the treatment group and five in the control group). All were thought to be unrelated to the study.</p> <p>Serious adverse events 55 serious adverse events were recorded in 44 patients. 14 in ten patients in the budesonide group and 41 events in 34 patients in the placebo group (p=0.001). None of the serious adverse events were believed to be related to treatment or treatment failure.</p> <p>Conclusion The study did not find an effect of long term treatment with inhaled corticosteroids on decline in lung function in patients with mild to moderate COPD.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	196

Author / Title / Reference / Yr	<p>Pauwels, R. A., Lofdahl, C. G., Laitinen, L. A., Schouten, J. P., POSTMA, D. S., Pride, N. B., & Ohlsson, S. V. 1999, "Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking", <i>New England Journal of Medicine</i>, vol. 340, no. 25, pp. 1948-1953. Ref ID: 195</p> <p>Pauwels, R. A., Lofdahl, C.-G., Pride, N. B., POSTMA, D. S., Laitinen, L. A., & Ohlsson, S. V. 1992, "European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): Hypothesis and design", <i>European Respiratory Journal</i>, vol. 5, no. 10, pp. 1254-1261. Ref ID: 1696</p> <p>Lofdahl, C. G., POSTMA, D. S., Laitinen, L. A., Ohlsson, S. V., Pauwels, R. A., & Pride, N. B. 1998, "The European respiratory society study on chronic obstructive pulmonary disease (EUROSCOP): Recruitment methods and strategies", <i>Respiratory Medicine</i>, vol. 92, no. 3, pp. 467-472. Ref ID: 1707</p>
N=	N=1277. Geographical location=9 European countries. Sites=39 centres. Duration=3 years (N=71% completed 3 years)
Research Design	<p>Parallel group double blind placebo controlled randomised multicenter study.</p> <p>Run in phase consisting of 3/12 smoking cessation program.</p> <p>In subjects who did not stop smoking, this phase was followed by a 3/12 period during which compliance with inhaled medication was assessed with the use of a placebo containing dry powder inhaler with a hidden mechanical counter.</p> <p>Participants who continued smoking and were at least 75% compliant were randomised.</p>
Aim	To elicit whether regular treatment with the inhaled glucocorticoid budesonide would reduce the decline in lung function in patients with mild COPD who continued smoking.
Operational Definition	<p>ATS criteria were used to determine FEV1.</p> <p>FEV1 post bronchodilator response between 50 to 100% of the predicted normal value.</p> <p>Pre bronchodilator FEV1 to slow vital capacity <70%</p> <p>The increase in FEV1 after inhalation of 1mg Terbutaline from dry powder inhaler <10% of the predicted normal value.</p> <p>The change in FEV1 between the end of the first 3/12 period of the run-in phase and the end of the second had to be <15%.</p>
Population	Mild COPD who continue smoking (asthmatics excluded)
Intervention	Twice daily treatment with 400ug of budesonide inhaled from dry powered inhaler for three years
Comparison	Placebo
Outcome	Primary outcome: Change over time in FEV1 after use of a bronchodilator.
Characteristics	<p>Persons 30 to 65 years were eligible. Mean age 52 years</p> <p>Smoking at least 5 cigarettes per day and had smoked for at least 10 years.</p> <p>Baseline FEV1 L (mean + SD) 2.54 +/- 0.64</p> <p>Mean FEV1 77% predicted</p> <p>Excluded: Those who had used oral glucocorticoids for more than 4wks during the preceding 6/12 / The use of inhaled</p>

	glucocorticoids other than the study medication, beta blockers, cromones or long acting inhaled beta2 adrenergic agonists.
Results	<p>Changes in FEV1 after bronchodilator use over time</p> <p>The median decline in the FEV1 after the use of a bronchodilator over the 3 yr period was 140ml in the budesonide group and 180ml in the placebo group (p=0.05).</p> <p>During the first 6/12 the FEV1 improved at the rate of 17ml per year in the budesonide group compared with a decline of 81ml per year in the placebo group (p<0.001).</p> <p>From 9/12 to the end of the treatment, there was no statistically significant difference in the rate of FEV1 decline between the two groups.</p> <p>Budesonide had a more beneficial effect in participants who had smoked less. Participants with a history of smoking that was at or below the median of 36 pack years at enrolment had a decrease in FEV1 of 190ml during placebo treatment and 120 ml during budesonide treatment p<0.001). The loss of FEV1 in 3 years among participants with more than 36 pack years of smoking was not statistically significant.</p> <p>Similar % of participants stopped smoking in both groups.</p> <p>Side Effects</p> <p>10% of participants in the budesonide group and 4% in the placebo group had bruises during the study (p<0.001).</p> <p>Bone density</p> <p>Was measured in N=194 participants. There were no significant changes over time and no significant effect of treatment on bone density. (See ID 1711 separate paper).</p> <p>Adverse Events</p> <p>Serious adverse events were equally distributed between the groups. None were statistically significant.</p> <p>Conclusion</p> <p>”In people with mild COPD who continue smoking, the use of inhaled budesonide is associated with a small one time improvement in lung function but does not appreciably affect the long-term progressive decline”.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	195

Author / Title / Reference / Yr	<p>Johnell, O., Pauwels, R., Lofdahl, C.-G., Laitinen, L. A., POSTMA, D. S., Pride, N. B., & Ohlsson, S. V. 2002, "Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler", <i>European Respiratory Journal</i>, vol. 19, no. 6, pp. 1058-1063. Ref ID: 1711</p> <p>This is a subgroup analysis of Pauwels, R. A., Lofdahl, C. G., Laitinen, L. A., Schouten, J. P., POSTMA, D. S., Pride, N. B., & Ohlsson, S. V. 1999, "Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking", <i>New England Journal of Medicine</i>, vol. 340, no. 25, pp. 1948-1953. Ref ID: 195 (EUROSCOP)</p>
N=	<p>Of the N=912 who completed the 3yrs of treatment, N=653 (N=322 in the budesonide group and N=331 in the placebo) had spinal XR taken at baseline and at the end of treatment and N=161 (N=82 in budesonide group and N=79 in the placebo) had DEXA.</p> <p>Geographical location=39 centres in nine European countries</p> <p>Duration= 3 years</p>
Research Design	<p>Parallel group double blind placebo controlled randomised multicentre study.</p> <p>Subgroup analysis</p>
Aim	<p>To study the effects of long term inhaled corticosteroid therapy on bone mineral density and vertebral fracture rates in patients with mild chronic obstructive pulmonary disease.</p>
Operational Definition	<p>ATS criteria were used to determine FEV1.</p> <p>FEV1 post bronchodilator response between 50 to 100% of the predicted normal value.</p> <p>Pre bronchodilator FEV1 to slow vital capacity <70%</p> <p>The increase in FEV1 after inhalation of 1mg Terbutaline from dry powder inhaler <10% of the predicted normal value.</p> <p>The change in FEV1 between the end of the first 3/12 period of the run-in phase and the end of the second had to be <15%.</p>
Population	Mild COPD
Intervention	Twice daily treatment with 400ug of budesonide inhaled from dry powered inhaler for three years
Comparison	Placebo
Outcome	Bone mineral density / spinal radiography / osteocalcin measurement
Characteristics	<p>Persons 30 to 65 years were eligible. Mean age 52 years</p> <p>Smoking at least 5 cigarettes per day and had smoked for at least 10 years.</p> <p>Baseline FEV1 L (mean + SD) 2.54 +/- 0.64</p> <p>Mean FEV1 77% predicted</p> <p>Excluded:</p> <p>Those who had used oral glucocorticoids for more than 4wks during the preceding 6/12.</p> <p>The use of inhaled glucocorticoids other than the study medication, beta blockers, cromones or long acting inhaled beta2 adrenergic agonists</p>

Results	<p>Bone mineral density measurements There were no significant differences in BMD at any site in budesonide treated patients compared with the placebo group.</p> <p>Vertebral fractures There was no significant difference in the incidence of new fractures between the groups.</p> <p>Osteocalcin concentrations There was no significant difference in serum osteocalcin concentrations between the groups after 3 yrs.</p> <p>Conclusion “The long term treatment with inhaled budesonide, at a dose of 800ug day has no significant effect on bone mineral density or fracture rate in patients with COPD”.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	1711

Author / Title / Reference / Yr	Jones, P.W., Willitis, L. R., Burge, P. S., Calverley, P. M. A., on behalf of the inhaled steroids in obstructive lung disease in Europe study investigators. (2003). Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. Eur Respir J, 21, 68-73.
N=	Total N=751 participants Location=UK Sites= 18 hospitals
Research Design	Post-hoc analysis of RCT randomised, double-blind, placebo-controlled, parallel-group design.
Aim	A post hoc analysis to determine whether existing criteria for disease severity identifies patients with a different probability of exacerbating and whether the effect of inhaled corticosteroids on acute exacerbations is influenced by disease severity are reported.
Operational Definition	Patients stratified into mild and moderate-to-severe COPD which was defined using the ATS criterion of forced expiratory volume in one second (FEV1) 50% predicted. Mild >50%, moderate to severe < 50%. An exacerbation was defined as “chest problems requiring treatment with antibiotics and/or oral corticosteroids”. Specific symptom criteria were not used. Exacerbations were recorded by patient self-report at 3-monthly intervals. Treatment of each exacerbation was recorded specifically whether the attending doctor prescribed antibiotics, oral corticosteroids or both. Exacerbation was defined as worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics, or both. Specific symptom criteria were not used.
Population	Mild and moderate to severe COPD (non asthmatic)
Intervention	Fluticasone Propionate (FP) N=376 FP 500ug via metered dose inhaler and Volumatic spacer device.

	N=195 FP mild COPD N=180 FP Moderate to severe
Comparison	Placebo N=375
Outcome	Number of exacerbations per year
Characteristics	<p>Patients using inhaled corticosteroids discontinued them and entered an 8-week run-in period. After this they were given two week trial of oral corticosteroids 0.6mg kg⁻¹ day⁻¹. Other medication continued throughout trial (equally distributed between the treatment groups).</p> <p>Moderate to severe FEV1<50% pred Age Placebo/FP 64yrs/64yrs Male % Placebo/FP 81/86 Atopy% 14/13 FEV1L Placebo/FP 1.0/1.0 FEV1 % pred Placebo/FP 39/39 % FEV1 reversibility Placebo/FP 4.1/4.2 Mild FEV1 >50% pred Age Placebo/FP 63yrs/63yrs Male % Placebo/FP 66/63 Atopy% 11/14 FEV1L Placebo/FP 1.6/1.6 FEV1 % pred Placebo/FP 62/62 % FEV1 reversibility Placebo/FP 4.8/4.6</p>
Results	<p>Number of exacerbations per year No significant difference between 2 groups for total number of exacerbations. Over the 3yr period 29% of the mild patients had no exacerbations at all, but this was seen in only 16% of those with moderate-to-severe disease. The median exacerbation rate in the combined treatment groups was significantly lower in the mild patients (0.93yr⁻¹) compared to those with moderate-to-severe disease (1.64yr⁻¹), p<0.0001.</p> <p>In the ITT population, there were fewer exacerbations in the FP-treated group (0.99 exacerbations yr⁻¹) compared with placebo (1.32 exacerbations yr⁻¹) p=0.026. The significant effect of FP was confined to the moderate-to-severe group: FP median 1.47 exacerbations yr⁻¹; placebo 1.75 exacerbations yr⁻¹, p<0.022. There was no statistically significant effect in the mild group (FP median 0.67 exacerbations yr⁻¹, p=0.45). The frequency of exacerbations in the two patient groups remained unchanged throughout the 3yrs of the study.</p> <p>Exacerbations treated with steroids In patients with moderate-to-severe disease. 52% had a corticosteroid-treated exacerbation compared to 30% of the mild group</p>

	<p>(p<0.0001). The rate of these exacerbations was significantly lower in FP-treated patients compared to placebo, p<0.001.</p> <p>Onset of first exacerbation No difference in time to first exacerbation was found between FP and placebo group.</p> <p>Reversibility and exacerbations To test the presence of subgroups of patients with a greater effect of inhaled corticosteroids, further post hoc analyses were carried out, dividing patients into those with greater or less reversibility to bronchodilator and those with greater or less response to prednisolone. No significant difference was found.</p> <p>Author's conclusion: Patients with moderate to severe COPD and a history of recent exacerbations appear to derive most benefit from FP treatment.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ib
NCC CC ID	1787

Author / Title / Reference / Yr	Burge, P. S., Calverley, P. M. A., Jones, P. W., Spencer, S., Anderson, J. A., on behalf of the ISOLDE Study Group. (2003). Prednisolone response in patients with chronic obstructive pulmonary disease: Results from the ISOLDE study. Thorax, 58, 1-5.
N=	N= 524 participants / Location=UK / Sites=18 hospitals
Research Design	Sub-analyses of ISOLDE RCT randomised double-blind control trial
Aim	“A trial of corticosteroids has been recommended for all patients with chronic obstructive pulmonary disease, with the subsequent “response” determining the treatment selected. This approach assumes that patients can be reliably divided into responder and non-responder groups.” This study examines the distribution of the spirometric response to prednisolone in a well-defined population of patients with non-asthmatic COPD, and its relationship with subsequent changes in FEV1, health status, and exacerbation rate over the following three years.
Operational Definition	Post-bronchodilator (400ug salbutamol) FEV1 was >0.81 and <85% predicted, and the ratio of FEV1 to forced vital capacity (FVC) was <70%. The FEV1 response to salbutamol was <10% predicted. Steroid responders are defined as patients with a response to prednisolone of >20% of baseline. The ATS defines responders as those with a response of >12% baseline and >200ml. These were termed the Callahan and ATS criteria, respectively, and were used to determine differences between steroid responders and non-responders.
Population	Adult non-asthmatic COPD patients N=524
Intervention	Oral prednisolone 0.6 mg/kg 14 days (before starting the randomised treatment of the ISOLDE trial)
Factor of interest	Responders/non-responders
Outcome	Response to 14 day course of oral steroids

	<p>Separation of corticosteroid responders from non-responders Effects of between visit FEV1 variability on prednisolone response Factors relating to FEV1 post-bronchodilator response to prednisolone Relationship between prednisolone response and FEV1 change over 3 years</p>
Characteristics	<p>Patients had a clinical diagnosis of non-asthmatic COPD, were aged 40-75 yrs and had a history of current or previous smoking. Nasal and ocular topical corticosteroids allowed as were methylxanthines and long acting bronchodilators. All patients were given salbutamol 200mg and ipratropium bromide 80mg to use as required throughout trial. 8 week run-in, no oral or inhaled corticosteroids taken. The results are confined to the 524 subjects who had taken at least 80% of the prednisolone treatment and had FEV1 readings unaffected by respiratory exacerbations.</p> <p>Age 64.0yrs Male % 78%</p> <p>FEV1 pre-bronchodilator (l) 1.23 FEV1 pre-bronchodilator (% predicted) 43.1 FEV1 post-bronchodilator (l) 1.40 FEV1 post-bronchodilator (% predicted) 49.3 FEV1 post-pre-bronchodilator (ml) 179 FVC post-bronchodilator (l) 3.32 FVC post-bronchodilator (% predicted) 92.0 TLCO (% predicted) 56.4</p>
Results	<p>Response to 14 day course of oral steroids The mean pre-bronchodilator FEV1 response to prednisolone was 69ml (95% CI 53 to 85) and the mean post-bronchodilator response was 60ml (95% CI 46 to 74).</p> <p>Separation of corticosteroid responders from non-responders The post-bronchodilator FEV1 response to prednisolone was unimodally distributed, which suggests that the definition of responders and non-responders is arbitrary. "Responders and non-responders were not significantly different at base-line in terms of age, atopy, sex, and pack years of smoking (p>0.05)".</p> <p>Effects of between visit FEV1 variability on prednisolone response In the 4 weeks immediately preceding the prednisolone trial, the mean FEV1 fell significantly more in the responder group than in the intermediate group and the group who deteriorated after prednisolone. Patients with a post-bronchodilator FEV1 response to prednisolone of >20% of baseline had a significantly greater fall in FEV1 during the run-in phase than those with a lower or negative response to prednisolone (p<0.01).</p> <p>Factors relating to FEV1 post-bronchodilator response to prednisolone Age, atopy, sex, baseline FEV1, and bronchodilator response were not significantly related to the response to prednisolone (p>0.05). However, the FEV1 response to prednisolone was greater in ex-smokers than in smokers (p<0.01). Smokers were significantly</p>

	<p>younger ($p < 0.001$) than the ex-smokers and differences in FEV1 indicated that they also had better lung function.</p> <p>Relationship between prednisolone response and FEV1 change over 3 years</p> <p>The response to prednisolone was unrelated to the subsequent change in FEV1 over the following 3 years.</p> <p>The significant effect of treatment on decline in health status was not predicted by the prednisolone response.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ib
NCC CC ID	1791

Author / Title / Reference / Yr	Sin, D. D., Man, S. F. P. (2003). Inhaled corticosteroids and survival in chronic obstructive pulmonary disease: Does the dose matter? <i>European Respiratory Journal</i> , 21, 260-266.
N=	Total N=6,740 patients Location=Alberta, Canada Duration=Study patients followed for 3 years following discharge from initial hospital for COPD or until death. Sites=3 database
Research Design	Cross-sectional retrospective “observational” study using existing databases: Canadian Institute for Health Information (CIHI), Ottawa, Canada database; the Alberta Vital Statistics database (mortality data); the Alberta Blue cross database (information on medications dispensed)
Aim	To investigate the dose/response relationship of inhaled corticosteroids and mortality rates in COPD/ long-term impact.
Operational Definition	ICD-9 classification for COPD; “moderate to severe COPD” previously hospitalised patients.
Population	COPD in adults, asthma excluded. Those recently hospitalised for an acute exacerbation.
Intervention	Inhaled corticosteroid dosage
Comparison	<p>Various dosages.</p> <p>Definition of dosage categories: not dispensed and low ($< 500 \text{ ug day}^{-1}$ beclomethasone or equivalent) medium (501-1,000 ug.day^{-1}), high ($> 1,000 \text{ ug.day}^{-1}$) and indeterminate dose. The last category contained patients who received only one dispensation of inhaled corticosteroids during the follow-up period.</p> <p>No dose N=3397; Low dose N=2011; Medium dose N=318; High dose N=413; Indeterminate N=601</p>

Outcome	Mortality
Characteristics	<ul style="list-style-type: none"> • At least one hospitalisation for COPD as the most responsible diagnosis. • ICD-9 classification for COPD • Concomitant medication included • Mean age yrs = no dose 77.4/low dose 75.2/medium dose 74.3/high dose 74.5/indeterminate dose 75.7 • Sex (male/female)=no dose (1855/1542)/low dose (1112/899)/ medium dose (176/142)/ high dose (221/192)/ indeterminate (297/304). • There were no significant differences in age, sex, and Charlson comorbidity score between those who received and did not receive inhaled corticosteroids. There were no significant differences in these parameters across different dose categories. • Patients on high-dose inhaled corticosteroids therapy were more likely to have received other pulmonary medications, including ipratropium bromide, oral corticosteroids and oral theophyllines. • Patients who die during index hospitalisation are excluded.
Results	<p>Mortality OVERALL MORTALITY RATE Therapy with inhaled corticosteroids was associated with 39% fewer deaths than in those not on these medications (RR 0.61, 95% CI 0.56-0.66). After adjustments for age, sex, comorbid conditions, ICU stay and use of other pulmonary medications, a 25% reduction in the overall mortality rate was observed in those who received inhaled corticosteroids compared to those who did not (RR 0.75, 95% CI 0.68-0.82).</p> <p>Low-dose therapy Patients dispensed low-dose therapy showed a 23% reduction in mortality rate compared to those who did not receive any inhaled corticosteroids (RR 0.77, 95% CI 0.69-0.86).</p> <p>Medium-dose therapy Those on medium-dose therapy experienced a 52% reduction (RR 0.48, 95% CI 0.37-0.63) .</p> <p>High-dose therapy Those on high-dose therapy experienced a 45% relative reduction (RR 0.55, 95% CI 0.44-0.69) compared to those who did not receive any inhaled corticosteroids.</p> <p>Indeterminate doses Patients on indeterminate doses did not experience any significant decline in all-cause mortality rate (RR 0.88, 95% CI 0.76-1.03; p=0.108).</p> <p>SUB GROUP ANALYSIS- AGED 65-74 YRS AND WITHOUT COMORBID CONDITIONS Even among the healthiest members of the cohort, inhaled corticosteroids were associated with a significant survival advantage. In those aged 65-74 yrs and without any comorbid conditions. it was found that inhaled corticosteroids were</p>

	<p>associated with a 37% relative reduction in all-cause mortality rate compared to no therapy (RR 0.63, 95% I 0.50-0.79).</p> <p>Low-dose therapy Low dose-therapy was associated with a 37% reduction (RR 0.63, 95% CI 0.49-0.82).</p> <p>Medium-dose therapy Medium- dose was associated with a 50% reduction (RR 0.50, 95% CI 0.30-0.83).</p> <p>High-dose therapy High-dose was associated with a 57% reduction (RR 0.43, 95% CI 0.27-0.70). Inhaled corticosteroids were associated with a 43% lower risk of mortality (RR 0.57, 95% CI 0.51-0.63). Using cut-offs of 6, 9 and 12 months made little difference to the overall findings (RR 0.57 for 6 months, 0.58 for 9 months and 0.58 for 12 months), suggesting that survivor treatment selection bias was not a significant concern in the analysis.</p> <p>Inhaled corticosteroids therapy was associated with a 30% risk reduction (RR 0.70, 95% CI 0.53-0.93) in pulmonary-specific mortality rate.</p>
SIGN Quality Rating	-
Hierarchy of Evidence Grading	III
NCC CC ID	19360

Section 7.6.2 Oral steroids

N=142 Literature search
N=123 Excluded from abstracts
N=19 Full papers ordered and of these;
N=6 Papers critically appraised
N=13 Papers excluded
N=0 Paper found on cross referencing

Author	Publication Date	ID	SIGN Grade	Hierarchy
Weiner et al	1999	1709	+	Ib
Callahan et al.	1991	99	++	Ia
Corden et al.	1998	1672	+	Ib
Weir et al.	1990	12	-	Ib
Weir et al.	1990	1710	-	Ib

Author / Title / Reference / Yr	Weiner, P., Weiner, M., Rabner, M., Waizman, J., Magadle, R., & Zamir, D. 1999, "The response to inhaled and oral steroids in patients with stable chronic obstructive pulmonary disease. [see comments.]", <i>Journal of Internal Medicine</i> , vol. 245, pp. 83-89. Ref ID: 1709
N=	Total N= 168 participants Location= Outpatient clinic- Hadera, Israel Sites=1
Research Design	RCT-randomised, placebo controlled, double-blind crossover study 6-week course of 800 µg day ⁻¹ of inhaled budesonide vs placebo 2 week washout period 6-week course of 1600 µg day ⁻¹ of inhaled budesonide vs 400 µg day ⁻¹ of inhaled budesonide + 2 of puffs placebo 2-week washout period 6-week course of 40mg prednisone vs placebo
Aim	To determine the rate of response to inhaled β-agonist, its ability to serve as a criterion for differentiating those who respond to 'regular' doses of inhaled steroids (800 µg day of inhaled budesonide) from other patients, and whether a higher dose 1600 µg day of inhaled budesonide) would result in a better improvement in clinical symptoms and pulmonary function.

	In addition the authors tried to determine the number of patients who will benefit from oral treatment corticosteroids.
Operational Definition	Spirometric evidence of chronic airflow limitation: FEV1<50% of predicted, FEV1/FVC<60%
Population	Stable COPD Non-responders to bronchodilators [β_2 -agonist- no patient had at least 20% increase in FEV1 following bronchodilators]: N=124 (76M, 48F) Responder to bronchodilators [β_2 -agonist- each patient had at least 20% increase in FEV1 following bronchodilators]: N=44 (26M, 18F)
Intervention	800 $\mu\text{g day}^{-1}$ of inhaled budesonide 1600 $\mu\text{g day}^{-1}$ of inhaled budesonide 40mg prednisone vs placebo
Comparison	Placebo
Outcome	FEV1
Characteristics	Mean age (non-responders/responders)=64.4yrs/66.1yrs Weight (non-responders/responders)=68.2kgs/69.7kgs Smoking history (packets per year) (non-responders/responders)=41.7/38.9 FEV1 Pre-bronchodilators (non-responders/responders)=1.28/1.40 Post-bronchodilators (non-responders/responders)=1.34/1.80 Mean increase in FEV1 (non-responders/responders)=4.7%/28.6%
Results	NB: Only results relevant to the research question under consideration are reported in the present table. Therefore results pertaining to inhaled budesonide alone are not recorded. The mean FEV1 did not change following the treatment period with prednisone 40mg day ⁻¹ (1.98 [2 wks]; 2.00 [4 wks]; 1.96 [6 wks] L in the responders to bronchodilators, and 1.48 [2 wks]; 1.48 [4 wks]; and 1.51 [6 wks] L in the non-responders to bronchodilators respectively) or placebo (1.37 [2 wks]; 1.41 [4 wks]; and 1.40 [6 wks] L in the responders to bronchodilators and 1.33 [2 wks]; 1.40 [4 wks]; 1.37 [6 wks] L in the non-responders to bronchodilators, respectively). 20 responders to bronchodilators (91%), who were also responders to inhaled steroids, maintained the improved FEV1 during the prednisone period as well. In the responders to bronchodilators/non-responders to inhaled steroids group, 3 patients (37.5%) improved their FEV1>20% and were defined as responders to oral steroids. All 8 non-responders to bronchodilators/responders to

	inhaled steroids were also responders to oral steroids, while 11 patients (13.5%) in the non-responders to bronchodilators/non-responders to inhaled steroids group could be defined as responders to oral steroids.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ib
NCC CC ID	1709

Author / Title / Reference / Yr	Callahan, C. M., Dittus, R. S., & Katz, B. P. 1991, "Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease. A meta-analysis.", <i>Annals of Internal Medicine</i> , vol. 114, no. 3, pp. 216-223. Ref ID: 99
N=	N=10 studies met all quality criteria. (A further N=5 studies met partial quality criteria). Authors developed a scheme for sensitivity analysis in which the quality criteria were relaxed sequentially to show the effect of including increasingly less rigorous studies on the overall results. N=445 participants Location= The study sites were primarily outpatient chest clinics associated with university hospitals in the United States or Great Britain. Trial durations ranged from 7 days to 8 weeks.
Research Design	Meta-analysis of N=10 RCT. Randomised, double-blind, placebo-controlled clinical trials
Aim	To evaluate the effectiveness of oral corticosteroid therapy in patients with stable chronic obstructive pulmonary disease.
Operational Definition	"All qualifying studies used both clinical and spirometric findings to document the diagnosis of COPD". No other information provided pertaining to operational definitions in relation to stable COPD. Individual trials variously defined patient response to therapy as a 15%, 20% or 30% improvement in baseline FEV1. Several studies reported group mean improvement in FEV1 with treatment compared with group mean improvement in FEV1 with placebo. Authors defined a patient response to therapy as a 20% or greater improvement in baseline FEV1.
Population	Stable COPD N=445 participants (excluding asthma and COPD exacerbations)
Intervention	Oral corticosteroids- treatment regimen was equivalent to prednisone 40mg/d for 14 days.
Comparison	Placebo
Outcome	Response to therapy –% increase in the baseline FEV1.
Characteristics	The overwhelming majority of patients enrolled in these studies were male, chronic smokers in their sixties, with a baseline FEV1 of approximately 1 litre. Mean age range: 58yrs-64yrs FEV1 range: 735mL-1240mL

	Range of N participants: 10–83 All studies allowed pts to continue their “routine medications” including oral and inhaled bronchodilators. Pts did not receive other steroid preparations during the study.
Results	When stable COPD patients receiving oral corticosteroid therapy are compared to patients receiving placebo the overall treatment effect size ranged from 0% to 56%. After applying a uniform definition of patient response and treatment effect size across all qualifying studies, this range fell to 0% to 38%. When patient response is defined as an FEV1 of 15% or greater improvement in baseline, FEV1 the overall treatment effect size is 10% (95% CI, 2% to 18%). When patient response is defined as an FEV1 of 30% or greater improvement in baseline, FEV1 the overall treatment effect size is 11% (95% CI, 3% to 19%).
SIGN Quality Rating	++
Hierarchy of Evidence Grading	Ia
Studies Included	N=10 studies met all quality criteria Beerel et al. 1971; Blair et al. 1984; Eliasson et al. 1986; Lam et al. 1983; Mendella et al. 1982; Mitchell et al. 1986; O’Reilly et al. 1982; Robertson et al. 1986; Shim et al. 1978; Strain et al. 1985 N=5 studies met partial quality criteria Freedman 1963, Fuleihan et al 1967, Harding et al 1978, Mitchell et al 1984, Stokes et al 1982
NCC CC ID	99

Author / Title / Reference / Yr	Corden, Z. & Rees, P. J. 1998, "The effect of oral corticosteroids on bronchodilator responses in COPD", <i>Respiratory Medicine</i> , vol. 92, no. 2, pp. 279-282. Ref ID: 1672
N=	Total N=18 participants Location=London UK Sites=1
Research Design	Randomised controlled, double-blind cross-over trial
Aim	To assess the effect of oral corticosteroids on bronchodilator responses in COPD.
Operational Definition	FEV1 <70% predicted and FEV1/FVC ratio <60%
Population	Moderate to severe COPD patients.
Intervention	Prednisolone N=18
Comparison	Placebo N=18

Outcome	FEV1 and FVC
Characteristics	FEV1 < 70%; FEV1/FVC ratio <60% Mean age=69.9yrs (56yrs-81yrs) Male/female N=16/2 Mean FEV1 baseline=0.86l
Results	<p>FEV1 and FVC measurements</p> <p>The only significant change in spirometry was an increase in FVC after prednisolone compared with initial values (salbutamol day, 0.33l 95% CI 0.06-0.60L, p=0.02; oxitropium day, 0.26l 95% CI -0.03 to +0.55L, =0.07).</p> <p>When the changes in FEV1 and FVC after prednisolone and placebo were examined, there were no significant differences. Absolute levels of FEV1 and FVC during the dose-response curves showed no significant differences between placebo and prednisolone periods. The maximal levels reached after prednisolone and placebo are not significantly different although in three of the four measurements the highest values occurred on prednisolone. At the maximum doses of oxitropium bromide differences between prednisolone and placebo periods were 0.001 for FEV1 (95% CI -0.07 to 0.08L) and 0.13L for FVC (95% CI -0.10 to +0.35 L). With salbutamol equivalent differences were 0.04 L for FEV1 (95% CI -0.05 to 0.13 L) and 0.18 L for FVC (95% CI -0.07 to +0.43 L).</p> <p>16 of 18 subjects produced adequate home recordings of spirometry throughout the 6 weeks of the study. There were no significant differences between the mean absolute FEV1 or FVC responses to oxitropium bromide during the last week of placebo and prednisolone treatment. The FEV1 increase after oxitropium was 0.12L on prednisolone and 0.14L on placebo (t=0.62, p=0.51; 95% CI of difference -0.14 to +0.10L). The FVC increases with oxitropium was 0.24L on prednisolone and 0.28L on placebo (t=0.17, p=0.26; 95% CI of difference -0.20 to +0.12L).</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ib
NCC CC ID	1672

Author / Title / Reference / Yr	Weir, D. C., Robertson, A. S., Gove, R. I., Burge, Sherwood, P. (1990). Time course of response to oral and inhaled corticosteroids in non-asthmatic chronic airflow obstruction. Thorax, 45, 118-121.
N=	Total N =121 participants / Location=Birmingham, UK / Sites=1
Research Design	RCT randomised double-blind double dummy crossover comparison. Inhaled beclomethasone dipropionate (500ug thrice daily), oral prednisolone (40mg/day) and placebo were compared on time taken to reach a plateau in PEF with treatment and time taken for PEF to return to pre-treatment levels after cessation of treatment- each was given for 14 days. with a 14-day washout period between treatments. The first treatment period was preceded by a four-week

	baseline period. Patients attended the laboratory on 1 and 14 days of the baseline period, and on the last day of each treatment period. 14 further patients who completed the same protocol without the placebo period are included in this analysis, as response to treatment has been defined without reference to the placebo period in view of the treatment effect noted in the trial.
Aim	To analyse the time course of the response to oral and inhaled corticosteroids by assessing the time taken to reach a plateau in PEF with treatment and the time taken for PEF to return to pre-treatment levels after cessation of treatment.
Operational Definition	Nil documented apart from “chronic airflow obstruction”
Population	Outpatients with chronic airflow obstruction of at least five years. (Asthmatics excluded)
Intervention	Oral prednisolone N=121 <i>In line with the study question addressed, reported results relate to prednisolone vs placebo only. Therefore, comparisons between prednisolone and beclomethasone have been omitted in this table.</i>
Comparison	Placebo N=121
Outcome	FEV1 & FVC - The mean of 3 technically satisfactory blows within 10% or 100 ml on a dry wedge spirometer was used for analyses. FEV1 and FVC were measured on two occasions during the baseline phase before any trial treatment was given, and on the final day of each treatment phase, all visits being at the same time of day. PEF – mini Wright’s peak flow meter. Best of at least three attempts with the highest two readings within 20 l/min. Baseline values were recorded during the 2 weeks before the first treatment phase, and the mean PEF was calculated over the final 7 days of this period.
Characteristics	No further demographic details available in this paper.
Results	A full response to treatment was defined as an improvement in absolute values of FEV1 or FVC of at least 20% measured on the last treatment day, or the same improvement in mean PEF over the final seven days of the treatment period, over the values obtained during the baseline period. A partial response was defined as improvement of at least 15% in one of these measurements or of at least 10% in any two measurements. Time course The time to peak effect with oral prednisolone varied from one to more than 14 days. In eight of the responses the daily mean PEF was still rising on the final day of the treatment period. A full or partial response to placebo treatment occurred in 24 of the 107 patients, only 5 showed a significant increase in daily mean PEF. The PEF response to placebo was less than the PEF response to the two active treatments ($\chi^2 = 12.1$, $p < 0.01$). Peak effect occurred on days 5, 7, 10 and 11 (2 subjects), and the time taken to return to pre-treatment levels (available for three responses) was one day (2 cases) and 5 days. Results are presented only as relevant to the question under consideration. Therefore inhaled beclomethasone results have been excluded.
SIGN Quality Rating	-

Hierarchy of Evidence Grading	Ib
NCC CC ID	12

Author / Title / Reference / Yr	Weir, D. C., Gove, R. I., Robertson, A. S., Burge, P. S. (1990). Corticosteroid trials in non-asthmatic chronic airflow obstruction: A comparison of oral prednisolone and inhaled beclomethasone dipropionate. <i>Thorax</i> , 45, 112-117.
N=	Total N= 107 participants Location=Outpatients, Birmingham, UK Sites=1
Research Design	RCT randomised, double blind, double dummy, placebo controlled, crossover trial. Each treatment was given for two weeks followed by a two-week washout period before the next treatment period. The first treatment period was preceded by a four-week baseline period. Patients attended the laboratory on days 1 and 14 of the baseline period for initial investigations, and on the last day of each treatment period for subsequent assessments.
Aim	To compare the response to oral prednisolone (40 mg/day) with that to inhaled beclomethasone dipropionate (500 µg thrice daily) in outpatients with non-asthmatic chronic airflow obstruction.
Operational Definition	FEV1 below 70% predicted. No internationally recognised operational definition provided e.g. not explicitly linked to ATS / BTS / ERS etc criteria.
Population	Outpatients with adult onset chronic airflow obstruction of at least five years duration and an.
Intervention	Prednisolone N=38 <i>In line with the study question addressed, reported results relate to prednisolone vs placebo only. Therefore, comparisons between prednisolone and beclomethasone have been omitted in this table.</i>
Comparison	Placebo N=35
Outcome	FEV1 & FVC – dry wedge (Vitalograph) spirometer. The mean of 3 technically satisfactory blows within 10% or 100 ml on a dry wedge spirometer was used for analyses. FEV1 and FVC were measured on two occasions during the baseline phase before any trial treatment was given, and on the final day of each treatment phase, all visits being at the same time of day. PEF – mini Wright’s peak flow meter. After the second baseline visit patients were asked to measure peak expiratory flow rate (with a mini Wright’s peak flow meter) four hourly during waking hours at home, and record best of at least three attempts with the highest two readings within 20 l/min. Baseline values were recorded during the 2 weeks before the first treatment phase, and the mean PEF was calculated over the final 7 days of this period.
Characteristics	Total sample baseline characteristics

	<p>No patient had received oral or inhaled corticosteroids in the preceding six months. Mean age= 62.9 yrs FEV1L=1.19 % predicted=44.2 Forced vital capacity % predicted=79.2 Total lung capacity % predicted=52.4 Residual volume % predicted=173.6 Number of: Current smokers=41 Ex-smokers=54 Lifelong non-smokers=12 Number with chronic bronchitis=77 (Medical Research council definition) Baseline characteristics of the group according to the treatment received in the first phase N Placebo/Prednisolone=35/38 Females Placebo/Prednisolone=7/7 FEV1L Placebo/Prednisolone=1.15/1.20 % predicted Placebo/Prednisolone=42.8/44.7 Cigarette years Placebo/Prednisolone=712/896 Current smokers Placebo/Prednisolone=11/7 Ex-smokers Placebo/Prednisolone=19/28 Lifelong non-smokers Placebo/Prednisolone=5/3</p>
<p>Results</p>	<p>There was a significant order effect in the response to placebo, in that the placebo response rate was greater when placebo had been preceded by active treatment ($p<0.05$); this was not seen with the response to prednisolone or to beclomethasone dipropionate ($p=0.02$). Because of this order effect, response to treatment was defined with respect to initial baseline values before any trial treatment had been given, and the two active treatments were compared with placebo by a parallel group analysis of the first treatment phase data.</p> <p>A full response to treatment was defined as an improvement in absolute values of FEV1 or FVC of at least 20% measured on the last treatment day, or the same improvement in mean PEF over the final seven days of the treatment period, over the values obtained during the baseline period.</p> <p>A partial response was defined as improvement of at least 15% in one of these measurements or of at least 10% in any two measurements.</p> <p>First treatment phase only FEVC1 & FVC - The number of patients showing a full response to prednisolone (16/38) was significantly greater than the number showing a similar response to placebo (3/35) ($p<0.005$). When partial responses are included in the analysis the response rate for oral prednisolone (17/38) was significantly greater than that for placebo (4/35; $p<0.002$). There was no significant difference</p>

	in the response to either active drug in this analysis either for full responders (p<0.1) or when full and partial responders were considered.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	Ib
NCC CC ID	1710

Section 7.7 Combination therapy

N= 437 Literature search
N=403 Excluded from abstracts
N=34 Full papers ordered and of these;
N= 17 papers critically appraised
N= 17 papers excluded
N=0 Paper found on cross referencing

Author	Publication Date	ID	SIGN Grade	Hierarchy
Beta2 Agonist and Anticholinergic				
Chapman	2002	1719	+	Ib
D'Urzo	2001	973	+	Ib
Cazzola	2000	975	-	Ib
van Noord	2000	175	+	Ib
Campbell	1999	826	-	Ib
Gross	1998	827	+	Ib
Auerbach	1997	830	+	Ib
Bone	1994	182	+	Ib
Beta2 Agonist and Theophylline				
ZuWallack	2001	1118	++	Ib

Anticholinergic and Theophylline				
Bellia	2002	1264	+	Ib
Friedman	1999	1720	+	Additional results from ref 182 and ref 830
Nishimura	1995	1722	+	Ib
Beta2 Agonist and Steroids				
Calverley	2003	1702	++	Ib
Szanfranski	2003	1698	++	Ib
Mahler	2002	1689	++	Ib
Papers with SIGN rating "minus"				
Taylor	1985	657	-	Ib
Karpel	1994	189	-	Ib

Author / Title / Reference / Yr	Chapman & Arvidsson, P. C. 2002, "The addition of Salmeterol 50 mg bid to anticholinergic treatment in patients with COPD: A randomized, placebo controlled trial", <i>Canadian Respiratory Journal</i> , vol. 9, pp. 178-185. Ref ID: 1719
N=	N= 408 Location= Canada, Denmark, the Netherlands, Russia, Sweden, UK Sites – 52 Duration – 6 months
Research Design	Randomised, double-blind, placebo-controlled parallel group trial.
Aim	To compare the effect of adding Salmeterol (50ug b.i.d.) or placebo to concurrent anticholinergic therapy on symptom scores, quality of life, prebronchodilator lung function and exacerbations in patients with moderately severe COPD
Operational Definition	FEV1 85% predicted, FEV1/FVC <70%
Population	<p>Inclusion COPD, 40 yrs or older, taking anticholinergic agents (alone or as combination) for at least 4 week, history of smoking equivalent to 10 pack years, sputum production on most days during last three consecutive months for two consecutive years, baseline FEV1 <85% predicted, baseline eFEV1/FVC < 70%, FEV1 reversibility 5 to 15% predicted, symptoms on at least 7 of previous 14 days and night periods of run-in phase.</p> <p>Exclusion: Respiratory infection requiring prescribed medication hospitalised for COPD within 4 weeks before start of run-in, concurrent respiratory disorders, pregnant or lactating women.</p>
Intervention	Salmeterol 50ug b.i.d via MDI (All other prescribed medications including anticholinergics for COPD permitted. Salbutamol given as rescue medication)
Comparison	Placebo b.i.d. via MDI (All other prescribed medications including anticholinergics for COPD permitted. Salbutamol given as rescue medication)

Outcome	Daily record cards to record morning and evening PEFR (in triplicate) and number of times rescue Salbutamol required, symptom scores (daytime and night time), adverse events, FEV1, exacerbation, SGRQ																
Characteristics	<table border="1" data-bbox="562 344 1912 507"> <thead> <tr> <th data-bbox="562 344 1010 376"></th> <th data-bbox="1010 344 1464 376">Salmeterol 50ug bid (n = 201)</th> <th data-bbox="1464 344 1912 376">Placebo (n = 207)</th> </tr> </thead> <tbody> <tr> <td data-bbox="562 376 1010 408">Sex male (%)</td> <td data-bbox="1010 376 1464 408">129 (64)</td> <td data-bbox="1464 376 1912 408">132 (64)</td> </tr> <tr> <td data-bbox="562 408 1010 440">Sex female (%)</td> <td data-bbox="1010 408 1464 440">72 (36)</td> <td data-bbox="1464 408 1912 440">75 (36)</td> </tr> <tr> <td data-bbox="562 440 1010 472">FEV1 (L)</td> <td data-bbox="1010 440 1464 472">1.19</td> <td data-bbox="1464 440 1912 472">1.28</td> </tr> <tr> <td data-bbox="562 472 1010 504">FEV1 % predicted</td> <td data-bbox="1010 472 1464 504">44</td> <td data-bbox="1464 472 1912 504">46</td> </tr> </tbody> </table> <p data-bbox="562 539 1995 571">No significant differences at baseline. Medication usage comparable among groups.</p>			Salmeterol 50ug bid (n = 201)	Placebo (n = 207)	Sex male (%)	129 (64)	132 (64)	Sex female (%)	72 (36)	75 (36)	FEV1 (L)	1.19	1.28	FEV1 % predicted	44	46
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Results	<p data-bbox="562 579 1995 611">Day- and night-time symptom scores No significant difference between groups</p> <p data-bbox="562 611 1995 643">Lung function Among treated-treated patients, morning pre-treatment FEV1 levels improved significantly above baseline levels. This effect persisted during the six-month treatment period. These improvements in lung function were significantly greater in the Salmeterol group than in the placebo group for all but the last clinic visit. Analysis of adjusted treatment differences showed that mean improvement over the 24-week period was significantly higher in the Salmeterol group than in the placebo group (p<0.01)</p> <p data-bbox="562 643 1995 675">Exacerbations and health care use During the treatment period, 26% of treated-treated patients and 33% of placebo-treated patients experienced at least one exacerbation of COPD (p=0.117) Fewer salmeterol-treated patients experienced more than 2 exacerbations (NS)</p> <p data-bbox="562 675 1995 707">Quality of life Scores for the SGRQ were reduced from baseline for all components of the questionnaire (symptoms, activity, impact on daily life) among patients in the Salmeterol group, with a significant improvement in the symptom component (p<0.005), the impact on daily life component (p = 0.05) and the total score (p<0.05) No significant difference between groups</p> <p data-bbox="562 707 1995 738">Safety Incidence of adverse events recorded during the study were similar for both treatment groups, with at least one adverse event being reported by 72% of patients in the Salmeterol group and 71% patients in the placebo group. Most common adverse events were related to the respiratory system in both treatment groups, with exacerbations of COPD being the most common event reported by 44 patients (22%) receiving placebo and 41 patients (20%) receiving Salmeterol. Events considered to be related to drug treatment were recorded in 11% of patients in the Salmeterol group and 10% of the patients in the placebo group.</p>																

	Conclusion Addition of Salmeterol 50ug b.i.d. to a regimen including anticholinergic agents significantly improved pre-bronchodilator lung function.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1719

Author / Title / Reference / Yr	D'Urzo, A. D., De, S., Ramirez-Rivera, A., Almeida, J., Sichletidis, L., Rapatz, G., Kottakis, J., & FOR, I. N. T. 2001, "In patients with COPD, treatment with a combination of formoterol and Ipratropium is more effective than a combination of Salbutamol and Ipratropium: a 3-week, randomized, double-blind, within-patient, multicenter study", <i>Chest</i> , vol. 119, no. 5, pp. 1347-1356. Ref ID: 973
N=	N= 172 Location=9 countries (Argentina, Canada, Greece, Italy, Mexico, Norway, Poland, Portugal, Spain) Sites – 24 Duration – 6 weeks
Research Design	Randomised, double blind, double dummy two period crossover trial
Aim	To compare the efficacy of adding formoterol or Salbutamol to regular Ipratropium bromide treatment in COPD patients whose conditions were sub optimally controlled with Ipratropium bromide alone.
Operational Definition	American Thoracic Society definition FEV1 <65% predicted normal and FEV1 <70% FVC
Population	Inclusion COPD according to ATS guidelines; age >40yrs; current or previous smokers (>10 pack years); FEV1 <65% predicted normal and FEV1 <70% FVC; increase in FEV1 of at least 5% baseline and <12% of predicted normal value with Salbutamol; total symptoms score from daily diary recordings of >1 on at least 3 of last 7 days; use of Ipratropium bromide for at least 1 month prior to screening visit. Exclusion Current or previous diagnosis of asthma, respiratory tract infection within 1 month previous, hospitalisation or emergency department treatment for acute COPD exacerbation with preceding month, need for long term oxygen therapy, QTc > 0.46s at screening visit, treatment with inhaled corticosteroids or oral xanthines started/discontinued/changed during previous month.
Intervention	Formoterol (12ug b.i.d. via dry powder inhaler) plus placebo Salbutamol in addition to Ipratropium bromide (40ug q.i.d via MDI) (3 weeks) followed by Salbutamol (200ug q.i.d via MDI) plus placebo formoterol in addition to Ipratropium bromide (40ug q.i.d via MDI) (3 weeks)
Comparison	Salbutamol plus placebo formoterol in addition to Ipratropium bromide (3 weeks) followed by Formoterol plus placebo Salbutamol in addition to Ipratropium bromide (3 weeks)

Outcome	Lung function: peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), impairment of daily activities (symptoms), quality of life, exacerbations and hospitalisations.															
Characteristics	<table border="1"> <tr> <td>Gender (M/F)</td> <td>128/31</td> </tr> <tr> <td>Age (y)</td> <td>65 (9.4)</td> </tr> <tr> <td>FEV1 before study drugs</td> <td>58.7 ± 23.8</td> </tr> <tr> <td>FVC before study drugs</td> <td>2.6 (0.71)</td> </tr> <tr> <td>Total symptom score (diary)</td> <td>5.9</td> </tr> <tr> <td>No of inhalations of rescues medication, puff/d</td> <td>1.9</td> </tr> <tr> <td>Concomitant medication No (%)</td> <td>Inhaled corticosteroids 65 (40.9) Oral Theophylline 15 (9.4) both 17 (10.7)</td> </tr> </table>	Gender (M/F)	128/31	Age (y)	65 (9.4)	FEV1 before study drugs	58.7 ± 23.8	FVC before study drugs	2.6 (0.71)	Total symptom score (diary)	5.9	No of inhalations of rescues medication, puff/d	1.9	Concomitant medication No (%)	Inhaled corticosteroids 65 (40.9) Oral Theophylline 15 (9.4) both 17 (10.7)	
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Concomitant medication No (%)	Inhaled corticosteroids 65 (40.9) Oral Theophylline 15 (9.4) both 17 (10.7)															
Results	<p>Morning premedication PEF ITT-1 – all randomised patients (n = 144) ITT-2 - no exacerbations (n = 31) ITT-3 - > 1 exacerbation (n = 113) The mean morning premedication PEF increased during both treatment periods; however the change in favour of Formoterol Ipratropium was statistically significant in all three ITT populations.</p> <p>ITT-1 PEF Formoterol/Ipratropium 15.1 ± 36.1 Salbutamol/Ipratropium 3.0 ± 43.1 FI – SI (95% CI) = 12.1 (5.6 – 18.6) (p = 0.0003)</p> <p>ITT-2 PEF Formoterol/Ipratropium 27.8 ± 27.2 Salbutamol/Ipratropium 18.1 ± 25.1 FI – SI (95% CI) = 9.5 (2.8 – 16.2) (p = 0.0073)</p> <p>ITT-3 PEF Formoterol/Ipratropium 11.6 ± 37.6 Salbutamol/Ipratropium –1.2 ± 46.1 FI – SI (95% CI) = 12.7 (4.6 – 20.8) (p = 0.0023)</p> <p>FEV1 and FVC ITT-1 all randomised patients Compared with baseline values, premedication FEV1 increased following 3 weeks treatment with Formoterol Ipratropium and decreased following treatment with Salbutamol Ipratropium. Estimated treatment difference was 0.116 L (p<0.0001)</p>															

	<p>Peak post medication FEV1 Occurred 2h after dosing with Formoterol Ipratropium Occurred 1h after dosing with Salbutamol Ipratropium Peak post medication FEV1 was significantly higher with formoterol/ipratropium than with salbutamol/ipratropium (p<0.0001) AUC of FEV1 for formoterol/ipratropium was much higher than for salbutamol/ipratropium (p<0.0001)</p> <p>FVC Difference between treatments in FVC was statistically significant at all time points – similar in profile to FEV1 (no data shown)</p> <p>Symptom scores and inhalation of rescue medication Mean total symptom score was 0.6 points lower with formoterol/ipratropium than with salbutamol/ipratropium (p = 0.0042) Mean number of inhalations of rescue medication during the last 7 days of each treatment period 1.3 for formoterol/ipratropium 1.5 for salbutamol/ipratropium Inhalations of rescue medication vs percentage of days 0 inhalations - ipratropium/formoterol (72.3%) salbutamol/ipratropium (68.8%) 1 to 2 inhalations – ipratropium/formoterol (7.4%) salbutamol/ipratropium (10.1%) 3 to 4 inhalation - ipratropium/formoterol (8.0%) salbutamol/ipratropium (8.9%) > 4 inhalations - ipratropium/formoterol (12.4%) salbutamol/ipratropium (12.2%)</p> <p>Quality of life measured by SGRQ All scores of the SGRQ domains and the “total” score were lower with formoterol/ipratropium than with salbutamol/ipratropium.</p> <p>COPD exacerbations No of patients with no COPD exacerbations during the treatment period was slightly higher with formoterol/ipratropium than with salbutamol/ipratropium: 55 patients (43.6%) and 49 patients (30.8%)</p> <p>Adverse events Sixteen patients (9.8%) had 19 adverse events with treatment with formoterol/ipratropium Twenty two patients (13.1%) had 34 adverse events with treatment with salbutamol/ipratropium Six patients (3.7%) reported respiratory system disorders with formoterol/ipratropium and 14 patients (8.3%) with salbutamol/ipratropium</p> <p>Drug related adverse events Formoterol/ipratropium – 3 adverse effects in three patients Salbutamol/ipratropium – 10 adverse effects in seven patients</p> <p>Conclusion The addition of formoterol to regular ipratropium treatment is more effective than addition of salbutamol</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b

NCC CC ID	973
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Author / Title / Reference / Yr	Cazzola, M., Di Lorenzo, G., & Di Perna, F. 2000, "Additive Effects of Salmeterol and Fluticasone or Theophylline in COPD", <i>Chest</i> , vol. 118, pp. 1576-1581. Ref ID: 975																							
N=	N= 80 Location = Italy Sites – Duration – 12 weeks																							
Research Design	Randomised parallel group trial																							
Aim	To investigate the potential additive effect of two different doses of inhaled Fluticasone propionate in patients with stable COPD who received Salmeterol, 50ug b.i.d., administered with a metered dose inhaler (MDI)																							
Operational Definition	American Thoracic Society criteria																							
Population	Well controlled COPD, who had previously been individually dose-titrated with slow-release Theophylline to a serum Theophylline level of 10-20ug/mL, >50yrs old with at least 20 year smoking history, a change in FEV1 < 12% as a percent of the predicted normal value following Salbutamol, postbronchodilator FEV1 <85% and good MDI technique. Exclusion: Current evidence of asthma as primary diagnosis; unstable respiratory disease requiring oral/parenteral corticosteroids within 4 weeks prior to beginning the study; upper or lower respiratory tract infection within 4 weeks of the screening visit; unstable angina or unstable arrhythmias; concurrent use of medications that affected COPD or interacted with methylxanthine products, such as macrolides or fluoroquinolones; and evidence of alcohol abuse																							
Intervention	Salmeterol 50ug plus Fluticasone propionate 250ug b.i.d or Salmeterol 50ug Fluticasone propionate 500ug b.i.d.																							
Comparison	Salmeterol 50ug Salmeterol 50ug plus titrated Theophylline b.i.d.																							
Outcome	FEV1, FVC																							
Characteristics	<table border="1"> <thead> <tr> <th>Variables</th> <th>Salmeterol 50ug b.i.d.</th> <th>Salmeterol 50ug and Fluticasone propionate 500ug b.i.d.</th> <th>Salmeterol 50ug and Fluticasone propionate 500ug b.i.d</th> <th>Salmeterol 50ug and titrated Theophylline b.i.d</th> </tr> </thead> <tbody> <tr> <td>Age, yr</td> <td>64.6 (62-67.2)</td> <td>63.7 (60.6 – 66.8)</td> <td>64.2 (61.2-67.2)</td> <td>64.7 (61.8-67.6)</td> </tr> <tr> <td>Sex, No.</td> <td>18 M and 2F</td> <td>20 M</td> <td>17 M and 3F</td> <td>18M and 2F</td> </tr> <tr> <td>Pack years</td> <td>45.1 (41-49)</td> <td>42.9 (39.1-46.8)</td> <td>44.4 (41.5-47.4)</td> <td>46.8</td> </tr> </tbody> </table>				Variables	Salmeterol 50ug b.i.d.	Salmeterol 50ug and Fluticasone propionate 500ug b.i.d.	Salmeterol 50ug and Fluticasone propionate 500ug b.i.d	Salmeterol 50ug and titrated Theophylline b.i.d	Age, yr	64.6 (62-67.2)	63.7 (60.6 – 66.8)	64.2 (61.2-67.2)	64.7 (61.8-67.6)	Sex, No.	18 M and 2F	20 M	17 M and 3F	18M and 2F	Pack years	45.1 (41-49)	42.9 (39.1-46.8)	44.4 (41.5-47.4)	46.8
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Sex, No.	18 M and 2F	20 M	17 M and 3F	18M and 2F																				
Pack years	45.1 (41-49)	42.9 (39.1-46.8)	44.4 (41.5-47.4)	46.8																				
Results	FEV1 No significant differences among baseline spirometric values of the four treatment groups (FEV1 p>0.05)																							

	<p>A gradual increase in FEV1 was observed with each of the four treatments. Maximum significant (p<0.05) increases in FEV1 over baseline values that were observed after 3 months of treatment were as follows: Salmeterol, 50ug b.i.d – 0.163L (95 CI 0.080 to 0.245 L) Salmeterol 50ug plus Fluticasone propionate 250ug b.i.d. – 0.188L (95% CI, 0.089 to 0.287 L) Salmeterol 50ug plus Fluticasone propionate 500ug b.i.d. – 0.239L (95% CI, 0.183 to 0.296 L) Salmeterol 50ug plus titrated Theophylline b.i.d. 0.157L (95% CI, 0.027 to 0.288) However, mean differences between groups in highest FEV1 were not significant. Only the dose response curve for Salbutamol in the group receiving Salmeterol 50ug, plus Fluticasone propionate, 500ug b.i.d. was significantly different (p<0.05) when data after 12 weeks of treatment was compared with those obtained after 8 weeks of treatment.</p> <p>FEV1 after inhalation of Salbutamol Mean FEV1 values after inhalation of Salbutamol, 800ug in all the four treatments were statistically different (p<0.05) from their corresponding pre-treatment levels after 12 weeks of treatment. After 12 weeks, Salbutamol 800ug induced the highest FEV1 improvement (0.283L; 95% CI, 0.106 to 0.459 L) in the patients receiving Salmeterol 50ug plus Fluticasone propionate 250ug b.i.d. and the lowest FEV1 improvement (0.152L; 95% CI, 0.065 to 0.283L) in those patients receiving Salmeterol 50ug. Patients receiving Salmeterol, 50ug, plus Fluticasone propionate 500ug b.i.d showed the highest mean improvement in FEV1 (0.472L; 95CI, 0.386 to 0.557L) over the presalbutamol baseline (pre-treatment) value; patients receiving Salmeterol, 50ug b.i.d. showed the lowest mean improvement in FEV1 *0.263L; 95% CI, 0.195 to 0.331L). The mean differences between the highest Salbutamol FEV1 after Salmeterol 50ug plus Fluticasone propionate 50ug b.i.d, and that after Salmeterol 50ug b.i.d were statistically significant (p<0.05)</p> <p>Conclusion Fluticasone propionate and Salmeterol given together are more effective than Salmeterol alone after a treatment period of 3 months.</p>
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1264

Author / Title / Reference / Yr	van Noord JA, de Munck DRAJ, Bantje TA, Hop WCJ, Akveld MLM, Bommer AM. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J 2000; 15: 878-885
N=	N= 144 Location= Netherland Sites – 3 Duration – 12 weeks
Research Design	Randomised, double-blind, double-placebo parallel group trial.
Aim	To compare the efficacy and safety of salmeterol either alone or in combination with ipratropium bromide with that of placebo in COPD patients.

Operational Definition	American Thoracic Society criteria																																		
Population	<p>Inclusion Current or ex-smokers with a smoking history equivalent to 10 pack-years and with COPD according to ATS criteria Aged 40-75 years No change in medication for COPD in preceding 6 weeks and no major changes in smoking habits during last 6 months FEV1 pred <75% predicted after inhalation of salbutamol FEV \leq65% of predicted normal and >0.75L at visit 1 or 2 FEV1/FVC ratio of <60% at visit1 or 2 Daytime symptom score of >2 on at least 4 out of 7 days during run-in period</p> <p>Exclusion: History of asthma, allergic rhinitis, atopy or total blood eosinophil count >500 clls/mm³, respiratory disease other than COPD, any clinically significant concurrent disease, oxygen therapy.</p>																																		
Intervention	Salmeterol 50ug plus ipratropium bromide 40ug (combination) q.i.d. (n = 47) <i>(Patients on stable dose of inhaled corticosteroids could continue treatment. Salbutamol given as rescue medication)</i>																																		
Comparison	Salmeterol 50ug plus ipratropium bromide matched placebo (salmeterol alone) b.i.d. (n = 47) Salmeterol-matched placebo plus ipratropium bromide- matched placebo (placebo) b.i.d. (n = 50) <i>(Patients on stable dose of inhaled corticosteroids could continue treatment. Salbutamol given as rescue medication)</i>																																		
Outcome	Lung function measured for 12 h after 1 st dose. Airway resistance (Raw), specific airway conductance (sGaw), FEV1 and FVC at baseline and 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12h after inhalation of the trial drug. Patient-recorded diary card recording morning and evening peak expiratory flow (PEF), daytime and night time symptoms and use of rescue salbutamol. Adverse events, exacerbations and withdrawals																																		
Characteristics	<table border="1"> <thead> <tr> <th></th> <th>Salmeterol plus ipratropium</th> <th>Salmeterol</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>Sex M/F %</td> <td>88/12</td> <td>89/11</td> <td>86/14</td> </tr> <tr> <td>Age yrs</td> <td>63 \pm 7</td> <td>65 \pm 6</td> <td>63 \pm 7</td> </tr> <tr> <td>FEV1 L</td> <td>1.2 \pm 0.4</td> <td>1.2 \pm 0.4</td> <td>1.1 \pm 0.3</td> </tr> <tr> <td>FEV1 %pred</td> <td>41 \pm 12</td> <td>42 \pm 10</td> <td>38 \pm 10</td> </tr> <tr> <td>FVC L</td> <td>3 \pm 8</td> <td>2.8 \pm 0.8</td> <td>2.8 \pm 0.7</td> </tr> <tr> <td>FEV1/FVC %</td> <td>42 \pm 9</td> <td>43 \pm 8</td> <td>41 \pm 9</td> </tr> <tr> <td>Raw kPa/L/s</td> <td>0.65 \pm 0.23</td> <td>0.63 \pm 0.23</td> <td>0.72 \pm 0.3</td> </tr> </tbody> </table>				Salmeterol plus ipratropium	Salmeterol	Placebo	Sex M/F %	88/12	89/11	86/14	Age yrs	63 \pm 7	65 \pm 6	63 \pm 7	FEV1 L	1.2 \pm 0.4	1.2 \pm 0.4	1.1 \pm 0.3	FEV1 %pred	41 \pm 12	42 \pm 10	38 \pm 10	FVC L	3 \pm 8	2.8 \pm 0.8	2.8 \pm 0.7	FEV1/FVC %	42 \pm 9	43 \pm 8	41 \pm 9	Raw kPa/L/s	0.65 \pm 0.23	0.63 \pm 0.23	0.72 \pm 0.3
	Salmeterol plus ipratropium	Salmeterol	Placebo																																
Sex M/F %	88/12	89/11	86/14																																
Age yrs	63 \pm 7	65 \pm 6	63 \pm 7																																
FEV1 L	1.2 \pm 0.4	1.2 \pm 0.4	1.1 \pm 0.3																																
FEV1 %pred	41 \pm 12	42 \pm 10	38 \pm 10																																
FVC L	3 \pm 8	2.8 \pm 0.8	2.8 \pm 0.7																																
FEV1/FVC %	42 \pm 9	43 \pm 8	41 \pm 9																																
Raw kPa/L/s	0.65 \pm 0.23	0.63 \pm 0.23	0.72 \pm 0.3																																

	sGaw kPa/L/s	0.33 ± 0.13	0.35 ± 0.18	0.29 ± 0.09
Results	No significant differences at baseline. Medication usage comparable among groups.			
<p>12 week treatment</p> <p>Symptom scores (day and night time)</p> <p>Throughout treatment</p> <p>Placebo group – decrease from 1.9 ± 0.1 to 1.7 ± 0.1 (NS)</p> <p>Salmeterol group – decrease from 2.0 ± 0.1 to 1.4 ± 0.1 (p<0.001)</p> <p>Combination group – decrease from 2 ± 0.1 to 1.3 ± 0.1 (p<0.001)</p> <p>Significant difference between change in daytime symptoms score between both salmeterol alone (p<0.005) and salmeterol + ipratropium (p<0.001) compared with placebo.</p> <p>No significant difference was seen between salmeterol and combination groups.</p> <p>Days with minimal symptoms (score <1)</p> <p>Combination therapy (run-in 14 ± 3.0% vs treatment 57 ± 3.0) (p<0.05)</p> <p>Salmeterol alone (run-in 14 ± 2.9% vs treatment 49 ± 3.0) (p<0.05)</p> <p>Placebo group (run-in 17 ± 3.7% vs treatment 34 ± 4.0) (p<0.05)</p> <p>Improvements in the combination group and salmeterol group were significantly better than in the placebo group (p<0.05)</p> <p>Nighttime symptom scores</p> <p>No differences were observed between the three groups throughout treatment</p> <p>Rescue medication</p> <p>Compared with placebo, treatment with both salmeterol and combination therapy were associated with a higher percentage of days and nights without use of additional salbutamol (p<0.01).</p> <p>No significant difference was observed between the two active treatments.</p> <p>Days with additional use of salbutamol</p> <p>Combination therapy (run-in 93 ± 3.2% vs treatment 27 ± 5.5)</p> <p>Salmeterol group (run-in 97 ± 2.2% vs treatment 34 ± 5.5)</p> <p>Placebo group (run-in 98 ± 1.8% vs treatment 74 ± 5.0)</p> <p>Nights with additional use of salbutamol</p> <p>Combination therapy (run-in 50 ± 6.9% vs treatment 24 ± 4.1)</p> <p>Salmeterol group (run-in 37 ± 6.3% vs treatment 17 ± 2.9)</p> <p>Placebo group (run-in 37 ± 6.1% vs treatment 33 ± 6.3)</p> <p>Peak expiratory flow</p> <p>Improvements in morning PEFs were significantly better in both active treatment groups than in the placebo group (p<0.001).</p> <p>No difference was observed between the salmeterol and combination treatment groups</p> <p>Morning PEF (L/min)</p>				

	<p>Combination therapy (run-in 252 ± 11 vs treatment 277 ± 23) ($p < 0.001$ compared with placebo)</p> <p>Salmeterol group (run-in 246 ± 9 vs treatment 262 ± 11) ($p < 0.001$ compared with placebo)</p> <p>Placebo group (run-in 238 ± 9 vs treatment 236 ± 9)</p> <p>Evening PEF</p> <p>Combination therapy (run-in 271 ± 11 vs treatment 297 ± 11) ($p < 0.01$ compared with salmeterol alone)</p> <p>Salmeterol group (run-in 257 ± 10 vs treatment 271 ± 11)</p> <p>Placebo group (run-in 259 ± 10 vs treatment 253 ± 10)</p> <p>FEV1</p> <p>During 12 week treatment</p> <p>Combination treatment – % increase $8 \pm 0.8\%$ pred ($p < 0.01$ vs salmeterol alone and vs placebo)</p> <p>Salmeterol group - % increase $5 \pm 0.9\%$ pred ($p < 0.01$ vs placebo)</p> <p>Placebo group - % increase $1 \pm 0.9\%$ pred</p> <p>FVC</p> <p>During 12 week treatment</p> <p>Combination treatment – % increase $12 \pm 1.2\%$ pred ($p < 0.01$ vs salmeterol alone and vs placebo)</p> <p>Salmeterol group - % increase $7 \pm 1.2\%$ pred (NS vs placebo)</p> <p>Placebo group - % increase $4 \pm 1.2\%$ pred</p> <p>sGaw</p> <p>Combination treatment – % decrease $61 \pm 6\%$ pred ($p < 0.01$ vs salmeterol alone and vs placebo)</p> <p>Salmeterol group - % decrease $36 \pm 6\%$ ($p < 0.01$ vs placebo)</p> <p>Placebo group - % decrease $16 \pm 6\%$ from baseline</p> <p>Adverse events</p> <p>No significant difference between groups.</p> <p>Most common adverse events were headache and cough.</p> <p>During 12 week treatment, 35 patients experienced a COPD exacerbation, 18 (36%) in the placebo group, 11 (23%) in the salmeterol group and six (13%) in the salmeterol and ipratropium group ($p < 0.01$ combination treatment vs placebo)</p> <p>Conclusion</p> <p>Over 12 weeks of treatment, a significant improvement in lung function (as measured by FEV1 and sGaw) was observed in both salmeterol alone group and the combination group. This improvement was greater following treatment with the combination therapy. In addition, the combination treatment produced a significant increase in FVC (airways obstruction) compared with both the salmeterol alone group and placebo. There was no difference between combination treatment and salmeterol in terms of symptom control and rescue medication.</p>
SIGN Quality Rating	+ (Blinded double critical appraisal)
Hierarchy of Evidence Grading	1b

NCC CC ID	175
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Author / Title / Reference / Yr	Campbell, S. 1999, "For COPD a combination of Ipratropium bromide and Albuterol sulfate is more effective than Albuterol base", <i>Archives of Internal Medicine</i> 25 JAN 1999 Vol 159(2) (pp 156-160), 1999. no. 2, pp. 156-160. Ref ID: 826
N=	N= 357 Location= US Sites –17 Duration – 29 days
Research Design	Prospective, randomised, double blind, and parallel group trial.
Aim	To compare the safety and efficacy of a combination aerosol containing Ipratropium bromide and Albuterol sulphate with Albuterol base in patients with COPD
Operational Definition	FEV \leq 65% of predicted normal and FEV1 \leq 70% FVC
Population	Inclusion Stable COPD > 40 years old, smoking history of more than 10 pack years and regularly using at least two prescribed therapeutic agents for control of COPD. Exclusion: History of asthma, allergic rhinitis or atopy, or with total blood eosinophil count above 500/mm ³
Intervention	Ipratropium bromide 36 μ g plus Albuterol 180 μ g four times daily (two extra doses per day were permitted to control symptoms) (Patients on stable dose of inhaled corticosteroids and/or Theophylline could continue treatment)
Comparison	Albuterol – 180 μ g four times daily (two extra doses per day were permitted to control symptoms) (Patients on stable dose of inhaled corticosteroids and/or Theophylline could continue treatment)
Outcome	Lung function testing on days 1 and 29 was conducted 15, 30 and 60 minutes after administration and hourly thereafter for total of 6h. Forced vital capacity (FVC), area under the curve (AUC), forced expiratory volume in 1 second, (FEV1), peak flow measurements. Biweekly severity of COPD symptoms (wheezing, shortness of breath, coughing, and tightness of chest) Patients symptoms graded from 0 (not present) to 3 (severe) Frequency of adverse events
Characteristics	251 men 103 women Mean age 65.6 years Mean duration of disease was 9.6 years (range 0.3 to 44 years) Mean FEV36.2% Mean ratio FEV1 to FVC was 36.1% 69% patients taking both an inhaled anticholinergics bronchodilators and inhaled B2 agonist prior to study. No comparison of baseline characteristics
Results	Efficacy FEV1

Both groups showed a clinically significant response to medication on each test day i.e. FEV1 of >15% over baseline

FEV1 response

Peak FEV1 responses (L)

Mean peak response for combination therapy was significantly greater than for the Albuterol group ($p < 0.05$, no baseline values, only adjusted mean peak change in FEV1 and FVC presented)

Adjusted mean peak changes in FEV1 and FVC

	Combination therapy (n = 176)	Albuterol (n = 180)
Day 1 FEV1	0.37	0.29
Day 29 FEV1	0.34	0.27
Day 1 FVC	0.77	0.65
Day 29 FVC	0.71	0.61

FEV1 Area under the curve

Mean AUC (0-6h) and AUC (0-4h) were significantly greater ($p < 0.05$) for combined therapy than for Albuterol on both test days, and the AUC (4-6h) was significantly greater on day 1 (*no data presented*)

Time to peak onset

Median time to peak was 1 hour for combined therapy and 30 minutes for Albuterol on both test days.

Duration of action

Median duration of action for the combined therapy group ranged from 3 to 4 hours; for Albuterol it was 2 hours.

Duration of action for combined therapy was significantly greater than for Albuterol on day 1 only.

Physicians global evaluations

No significant difference between groups

Symptoms

Statistically significant differences in favour of combination therapy were noted for wheezing and shortness of breath on days 1 to 29.

Statistically significant difference in favour of combination therapy was noted for tightness of chest on days 1 to 14.

Adverse events

No significant differences between groups.

During treatment 25.4% of patients receiving combination therapy and 33.3% of patients receiving Albuterol therapy reported adverse events or worsening of pre-existing condition that was present at baseline.

Conclusion

Combination of Ipratropium and Albuterol elicited a statistically greater bronchodilator response (peak FEV and FVC) compared with either agent alone.

SIGN Quality Rating
Hierarchy of Evidence Grading

- (Blinded double critical appraisal)
1b

NCC CC ID	826
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Author / Title / Reference / Yr	Gross, N., TASHKIN, D., Miller, R., Oren, J., Coleman, W., Linberg, S., Auerbach, D., Amin, D., Averill, F., Berman, B., Bleeker, E., Branditz, F., Brofman, J., Broughton, J. O., Brown, R., Candal, F., Chausow, A. M., Chinsky, K., Cordasco, E., DeGraff, A., Jr., Dewan, N. A., Derdak, S., Economau, P., Feldman, N. T., Fogarty, C., Goetter, W. E., Goldfarb, L., Good, J. T., Hynes, B., Heinz, G., Hughes, J., James, D. L., Karetzky, M., Karlsberg, R., Kerzner, B., Kirschner, E., Komadina, K., Krichbaum, D., Larimer, R., Lipetz, R., Lippman, M., LITTNER, M., Marinelli, C. T., Memon, N., Meyer, D., Mullican, W. S., Novack, D., Oliver, G., Opipari, M., Patrick, H., Piquette, C., Santiago, S., Sindel, L. J., Stoltz, R., Suen, J., Tidman, R., Tillis, W., Traub, S., Wainz, R., Wellman, J., Weltman, J., Westerman, J., Winn, R., & Wool, S. 1998, "Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease", <i>Respiration</i> , vol. 65, no. 5, pp. 354-362. Ref ID: 827
N=	N= 863 Location=US Sites – 60 Duration – 12 weeks
Research Design	Randomised, double-blind, controlled trial. Safety and efficacy of three study medications, albuterol sulfate, ipratropium bromide and a combination of the two delivered by nebulisation were compared initially after 2 weeks on each of the double-blind study medications during the crossover phase of the trial, and secondarily after up to 6 weeks on one of the randomised, double-blind study medications during the subsequent parallel phase of the trial.
Aim	To determine the effectiveness of an albuterol-ipratropium solution aerosol combination compared with solution aerosols of both component medications administered alone in patients with COPD.
Operational Definition	Diagnosis of COPD with FEV1 between 25 and 65% of normal predicted value
Population	Diagnosis of COPD with FEV1 between 25 and 65% of normal predicted value, > 40 years old, regular users of one or more bronchodilators for a minimum of 3 months prior to enrollment, to have a smoking history of at least 10 pack years. Exclusion: Anthraxosis, silicosis, any parenchymal disease not attributable to COPD, polycythemia, cor pulmonale, hypoxia, or a primary diagnosis that was attributable to allergic rhinitis, atopy or asthma; patients with clinically significant obstructive urinary disease, narrow-angle glaucoma, unstable angina pectoris or myocardial infarction in the past 6 months, known drug abuse within the past 12 months, or hospitalisation for pulmonary exacerbation within the last 2 months were excluded from participation; patients with a known hypersensitivity to any component of the study medications and patients who had received an investigational drug within 30 days preceding their first dose of study medication; pregnant or lactating patients, patients of childbearing potential (permitted if using contraceptive)
Intervention	50ug ipratropium and 250ug albuterol 4 times daily using nebuliser and compressor.
Comparison	50ug ipratropium or

	250ug albuterol 4 times daily using nebuliser and compressor																																																																					
Outcome	<p>Primary efficacy variable: change from pre-dose to peak FEV1 measured within 8h after dosing, following 2 weeks of treatment with each of the 3 study medications (on treatment days 14,28 and 42)</p> <p>Secondary efficacy variables: change from pre-dose to peak FEV1 measured within 7 h after dosing on day 84, FVC and FEV1-AUC and 6 minute walk, adverse events</p>																																																																					
Characteristics	<p>Male 533 female 330</p> <p>Age mean 66.3 range 40-93</p> <p>FEV1, L mean 1.145 range 0.4-3.330</p> <p>FEV1/FVC, % mean 48.1 range 19-90</p> <p>Patient demographics and baseline characteristics of all randomised patients were found to be similar across the 6 treatment sequences in the crossover phase of the trial and among the three treatment groups in the parallel phase.</p>																																																																					
Results	<p>Efficacy during crossover phase</p> <p>A total of 663 patients received combination treatment and at least one other study medication</p> <table border="1" data-bbox="562 695 1912 1139"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="4">Dey combination (DCS) versus albuterol</th> <th colspan="4">Dey combination (DCS) versus ipratropium</th> </tr> <tr> <th>n</th> <th>DCS mean</th> <th>albuterol mean</th> <th>p value</th> <th>n</th> <th>DCS mean</th> <th>ipratropium mean</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>Peak FEV1, l</td> <td>647</td> <td>0.387</td> <td>0.313</td> <td><0.001</td> <td>647</td> <td>0.387</td> <td>0.282</td> <td><0.001</td> </tr> <tr> <td>FEV-AUC (0-8h), l/h</td> <td>647</td> <td>1.495</td> <td>1.147</td> <td><0.001</td> <td>647</td> <td>1.503</td> <td>1.137</td> <td><0.001</td> </tr> <tr> <td>Time to peak FEV1, h</td> <td>634</td> <td>1.5</td> <td>1.5</td> <td>0.128</td> <td>625</td> <td>1.5</td> <td>2.1</td> <td><0.001</td> </tr> <tr> <td>Duration of >15% response in FEV,h</td> <td>361</td> <td>4.3</td> <td>3.7</td> <td><0.001</td> <td>297</td> <td>4.3</td> <td>4.1</td> <td>0.080</td> </tr> <tr> <td>6 minute walking distance</td> <td>631</td> <td>341.5</td> <td>341.3</td> <td>0.952</td> <td>638</td> <td>342.4</td> <td>340.5</td> <td>0.566</td> </tr> </tbody> </table> <p>Change from pre-dose to peak FEV1 measured within 8h after dosing</p> <p>Combination vs albuterol 0.387 l vs 0.313 l in the same subjects Difference = 0.074 l (p<0.001) (23.6%)</p> <p>Combination vs ipratropium 0.387 l vs 0.282 l in the same subjects</p>								Parameter	Dey combination (DCS) versus albuterol				Dey combination (DCS) versus ipratropium				n	DCS mean	albuterol mean	p value	n	DCS mean	ipratropium mean	p value	Peak FEV1, l	647	0.387	0.313	<0.001	647	0.387	0.282	<0.001	FEV-AUC (0-8h), l/h	647	1.495	1.147	<0.001	647	1.503	1.137	<0.001	Time to peak FEV1, h	634	1.5	1.5	0.128	625	1.5	2.1	<0.001	Duration of >15% response in FEV,h	361	4.3	3.7	<0.001	297	4.3	4.1	0.080	6 minute walking distance	631	341.5	341.3	0.952	638	342.4	340.5	0.566
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Difference = 0.106 l (p<0.001) (37.2%)

Using treatment, period, treatment by period interaction, treatment sequence, and patient as independent variables analyses confirmed significant treatment effects and found no treatment by period interaction or treatment sequence effects.

Using pretreatment baseline FEV1 and treatment sequence as covariates analysis confirmed pretreatment baseline FEV1 had a significant negative correlation with response (i.e. the lower a patient's baseline FEV1 the greater the response).

Subgroup analyses of peak FEV1 were also conducted to examine the effect of gender and age. The combination of ipratropium and albuterol was superior to both albuterol and ipratropium alone in both males and females (p<0.001). In addition, the combination was superior to both individual components in patients over and under the age of 65 (p<0.001).

Post-hoc analysis indicated that the response to albuterol alone was significantly greater than the response to ipratropium alone (p<0.05)

FEV1-AUC (0-8h)

Combination vs ipratropium

1.503 l/h vs 1.137 l/h

Combination vs albuterol

1.495 vs 1.147 l/h

Combination was significantly superior to albuterol or ipratropium alone (p<0.001)

Time to peak FEV1

Combination vs ipratropium

Combination was significantly superior to ipratropium (p<0.001)

1.5h vs 2.1h

Combination vs albuterol

No significant difference compared with albuterol alone

Duration of >15% response in FEV1, h

Combination vs ipratropium

No significant difference compared with ipratropium

Combination vs albuterol

4.3h vs 3.7h

Combination was significantly superior to albuterol (p<0.001)

Distance walked in 6 minutes

No significant differences between treatment groups

Efficacy during parallel phase

Results for parallel phase yielded results essentially identical to the crossover phase.

Peak FEV1 and FEV1-AUC and FVC

Combination maintained same magnitude of superiority over each component medication alone for all intervals tested.

Time to peak FEV1 response and duration of a 15% improvement in response

	<p>Similar magnitude and same direction as those measured during crossover phase but did not reach same level of significance (data not shown)</p> <p>6 minute walking distance No significant differences between treatment groups.</p> <p>Safety No significant differences between combination and either component in incidence of patients with adverse events across body systems.</p> <p>Conclusion Combination treatment of albuterol and ipratropium produces a statistically greater bronchodilator response compared with either component medication alone. A slight decrease in response to medication was seen over the study. All treatment regimens were similarly tolerated.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	827

Author / Title / Reference / Yr	Auerbach, D., Hill, C., Baughman, R., BOYARS, M., Braun, S., Buist, A. S., Campbell, S. C., CHICK, T., Cohen, B., Colice, G., Dunn, L., Friedman, M., Gilman, M., Gorin, A., Gross, N., Jenkinson, S., LEVINE, B., Libert, R., Liu, J., Mestas, G., O'Connor, R., Ramsdell, J., Rowlands, J., Serby, C. W., Warmer, A., Weiss, S., & COMBIVENT Inhalation Solution Study Group 1997, "Routine nebulized ipratropium and albuterol together are better than either alone in COPD", <i>Chest</i> , vol. 112, no. 6, pp. 1514-1521. Ref ID: 830
N=	N= 652 Location= US Sites – 25 Duration – 85 days
Research Design	Randomised, double blind, parallel group trial.
Aim	To examine whether long-term administration of combined albuterol and ipratropium delivered in one inhalation aerosol would results in greater bronchodilation in patients with COPD than the use of either agent alone.
Operational Definition	FEV \leq 65% of predicted normal and FEV1 \leq 70% FVC
Population	<p>Inclusion Stable COPD > 40 years old, smoking history of more than 10 pack years and regularly using at least two prescribed therapeutic agents for control of COPD.</p> <p>Exclusion: History of asthma, allergic rhinitis or atopy, or with total blood eosinophil count above 500/mm³</p>
Intervention	Ipratropium bromide 50µg plus albuterol 399µg three times daily (n=222) (two extra doses per day were permitted to control symptoms) (Patients on stable dose of inhaled corticosteroids and/or theophylline could continue treatment)

	Delivered by small volume nebuliser																																																																
Comparison	Ipratropium bromide – 50ug three times daily (n = 214) Albuterol – 300ug three times daily (n = 216) (Two extra doses per day were permitted to control symptoms) (Patients on stable dose of inhaled corticosteroids and/or theophylline could continue treatment) Delivered by small volume nebuliser																																																																
Outcome	Lung function testing on days 1, 29, 57, and 85 immediately before administration, 15, 30 and 60 min after drug administration and hourly thereafter for total of 8h. forced vital capacity (FVC), area under the curve (AUC), forced expiratory volume in 1 second, (FEV1), peak flow measurements. Severity of COPD symptoms (wheezing, shortness of breath, coughing, and tightness of chest) Global evaluation of patient condition subjectively assessed by investigator. Quality of life questionnaire evaluating dyspnoea, fatigue, emotional function and mastery.																																																																
Characteristics	<table border="1"> <thead> <tr> <th></th> <th>Ipratropium + Albuterol</th> <th>Ipratropium</th> <th>Albuterol</th> <th>Overall</th> </tr> </thead> <tbody> <tr> <td>Randomised and treated</td> <td>222</td> <td>214</td> <td>216</td> <td>652</td> </tr> <tr> <td>Age, yr (mean)</td> <td>65.5</td> <td>64.8</td> <td>64.6</td> <td>64.0</td> </tr> <tr> <td>Age, yr (range)</td> <td>41-83</td> <td>44-86</td> <td>41-85</td> <td>41-86</td> </tr> <tr> <td>Sex male</td> <td>146</td> <td>136</td> <td>142</td> <td>424</td> </tr> <tr> <td>Sex female</td> <td>76</td> <td>78</td> <td>74</td> <td>228</td> </tr> <tr> <td>FEV1 L mean</td> <td>0.918</td> <td>0.907</td> <td>0.910</td> <td>0.912</td> </tr> <tr> <td>FEV1 L range</td> <td>0.30-2.49</td> <td>0.18-2.11</td> <td>0.21-2.18</td> <td>0.18-2.49</td> </tr> <tr> <td>% pred FEV1 mean</td> <td>34.9%</td> <td>34.1</td> <td>34.1</td> <td>34.4</td> </tr> <tr> <td>% pred FEV1 range</td> <td>11.1-64%</td> <td>9.4-69.9</td> <td>9.2-64.4</td> <td>9.2-64.4</td> </tr> <tr> <td>FEV1/FVC mean</td> <td>44.1%</td> <td>43.7</td> <td>44.2</td> <td>44</td> </tr> <tr> <td>FEV1/FVC range</td> <td>21.3-78.7%</td> <td>18.4-77</td> <td>23.4-81.3</td> <td>18.4-81.3</td> </tr> </tbody> </table>						Ipratropium + Albuterol	Ipratropium	Albuterol	Overall	Randomised and treated	222	214	216	652	Age, yr (mean)	65.5	64.8	64.6	64.0	Age, yr (range)	41-83	44-86	41-85	41-86	Sex male	146	136	142	424	Sex female	76	78	74	228	FEV1 L mean	0.918	0.907	0.910	0.912	FEV1 L range	0.30-2.49	0.18-2.11	0.21-2.18	0.18-2.49	% pred FEV1 mean	34.9%	34.1	34.1	34.4	% pred FEV1 range	11.1-64%	9.4-69.9	9.2-64.4	9.2-64.4	FEV1/FVC mean	44.1%	43.7	44.2	44	FEV1/FVC range	21.3-78.7%	18.4-77	23.4-81.3	18.4-81.3
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Mean peak responses to the combination were significantly greater than those to each of the components on all 4 test days.
 Mean peak % increases in FEV1 over baseline on the 4 test days were
 Ipratropium + Albuterol – 34-37%
 Ipratropium alone – 27-29%
 Albuterol alone – 27-31%

Day	Ipratropium + Albuterol	Ipratropium	Albuterol
1	0.37	0.29 (p<0.001)	0.31 (p = 0.002)
29	0.34	0.29 (p=0.004)	0.29 (p = 0.013)
57	0.34	0.27 (p=<0.001)	0.27 (p<0.001)
85	0.34	0.27(p = <0.001)	0.29 (p=0.001)

FEV1 Area under the curve

The mean response to combination treatment was significantly greater than the response to each of the components during the first 4h on all test days.

8 h test period

Combination treatment and Ipratropium

Statistically significant difference on day 1
 No significant difference on days, 29, 57 and 85

Combination treatment and Albuterol

Statistically significant difference on days 1, 57 and 85.
 No significant difference on day 29

Duration of effect

Combination group - 3 to 5h
 Ipratropium group - 4h (p<0.05 on day 1 compared with combination)
 Albuterol group – 2 to 3 h (Significant difference on day 1 and 57 compared with combination)

Peak expiratory flow rate (PEFR)

Morning PEFR did not differ significantly between groups and did not change during the study.
 Evening PEFR values in the combination therapy group were significantly greater than those for the Albuterol group. (no data shown)

Physicians global evaluations (subjective rating)

Global evaluations were similar for all three treatment groups.

Symptom scores

COPD symptom scores did not change and did not differ between treatment groups.

Total number of patients days (%) of increased steroid medication

1.1% – combination group
 0.7% – Ipratropium group

	<p>1.4% – Albuterol group</p> <p>Addition of concomitant respiratory medication</p> <p>No significant difference between groups in use of concomitant respiratory medication</p> <p>Adverse events (drug related)</p> <p>24 patients - combination</p> <p>17 patients - Ipratropium</p> <p>24 patients - Albuterol</p> <p>Conclusion</p> <p>Combination of Ipratropium and Albuterol elicited a statistically greater bronchodilator response (peak FEV and FVC) compared with either agent alone.</p>
SIGN Quality Rating	+ (Blinded double critical appraisal)
Hierarchy of Evidence Grading	1b
NCC CC ID	830

Author / Title / Reference / Yr	Bone, R., Boyares, M., Braun, S. R., Buist, S., Campbell, S., Chick, T., Cohen, B. M., Conway, W., Cugell, D. W., Degraff, A., Friedman, M., George, R. B., Gershwin, E., Kram, J. A., Lakshminarayan, S., Levin, D. C., Levine, B., Petty, T. L., Rennard, S., Repsher, L., Sahn, S. A., Sandhaus, R., Serby, C. W., Simon, R. A., Tashkin, D., & Combivent Inhalation Aerosol Study Group 1994, "In Chronic obstructive pulmonary-disease, a combination of ipratropium and albuterol is more effective than either agent alone – An 85-day multicenter trial", <i>Chest</i> , vol. 105, no. 5, pp. 1411-1419. Ref ID: 182
N=	N= 534 Location= US Sites – 24 Duration – 12 weeks
Research Design	Randomised, double blind, parallel group trial.
Aim	To examine whether long-term administration of combined Albuterol and Ipratropium delivered in one inhalation aerosol would results in greater bronchodilation in patients with COPD than the use of either agent alone.
Operational Definition	FEV \leq 65% of predicted normal and FEV1 \leq 70% FVC
Population	<p>Inclusion</p> <p>Stable COPD > 40 years old, smoking history of more than 10 pack years and regularly using at least two prescribed therapeutic agents for control of COPD.</p> <p>Exclusion:</p> <p>History of asthma, allergic rhinitis or atopy, or with total blood eosinophil count above 500/mm³</p> <p>Patients who required more than 10 mg of oral prednisone daily within a month before entry into the study</p>
Intervention	Ipratropium bromide 42µg plus Albuterol 200µg four times daily (two extra doses per day were permitted to control symptoms)

	<i>(Patients on stable dose of inhaled corticosteroids and/or Theophylline could continue treatment)</i> Metered dose inhaler				
Comparison	Ipratropium bromide – dose 42ug four times daily Albuterol – dose 200ug four times daily Metered dose inhaler <i>(Patients on stable dose of inhaled corticosteroids and/or Theophylline could continue treatment)</i>				
Outcome	Lung function testing on days 1, 29, 57, and 85 immediately before administration and hourly thereafter for total of 8h. Forced vital capacity (FVC), area under the curve (AUC), forced expiratory volume in 1 second, (FEV1), peak flow measurements. Severity of COPD symptoms (wheezing, shortness of breath, coughing, and tightness of chest) Global evaluation of patient condition subjectively assessed by investigator.				
Characteristics		Ipratropium + Albuterol	Ipratropium	Albuterol	Overall
	Randomised and treated	182	179	173	534
	Age, yr (mean)	63.4	63.3	63.6	63.4
	Age, yr (range)	40-88	42-82	44-82	40-88
	Sex male	116	120	112	348
	Sex female	66	59	61	186
	FEV1 L mean	0.996	0.998	0.987	0.991
	FEV1 L range	0.38-2.31	0.29-2.78	0.32-2.43	0.29-2.78
	% pred FEV1 mean	37.4%	36.6	36.8	36.9
	% pred FEV1 range	11.9-76.2%	12.4-73.2	11.5-74.1	11.5-76.2
	FEV1/FVC mean	44%	44.4	43.5	44
	FEV1/FVC range	21.2-79.3%	22.6-69.4	20-92.8	20-92.8
Results	<p>Efficacy</p> <p>FEV1 No significant change in mean baseline FEV1 values was seen throughout the study. No significant differences in mean baseline FEV1 were seen between groups.</p> <p>FEV1 response Clinically significant mean FEV1 response (>15% above baseline) was observed in all three treatment groups on all 4 test days.</p> <p>Peak FEV1 responses (L) Mean peak responses to the combination were significantly greater than those to each of the components on all 4 test days. Mean peak % increases in FEV1 over baseline on the 4 test days were</p>				

Ipratropium + Albuterol – 31-33%

Ipratropium alone – 24-25%

Albuterol alone – 24-27%

Day	Ipratropium + Albuterol	Ipratropium	Albuterol
1	0.39	0.30 (p<0.001)	0.33 (p = 0.004)
29	0.36	0.31 (p=0.015)	0.3 (p = 0.007)
57	0.37	0.3 (p=0.001)	0.3 (p = 0.001)
85	0.37	0.3 (p = 0.001)	0.29 (p<0.001)

FEV1 Area under the curve

The mean response to combination treatment was significantly greater than the response to each of the components during the first 4h on all test days and during the fourth to sixth hours on the first test day.

8 h test period

Combination treatment and Ipratropium

Statistically significant difference on day 1

No significant difference on days, 29, 57 and 85

Combination treatment and Albuterol

Statistically significant difference on days 1, 57 and 85.

No significant difference on day 29

Duration of effect

Combination group - 4 to 5h

Ipratropium group - 4h (NS compared with combination)

Albuterol group – 2 to 3 h (Significant difference on all test days compared with combination)

FVC and FEF25-75%

Overall FVC response to the drug combination was significantly greater than the response to either Ipratropium or Albuterol alone (p<0.01 to p=0.04)

Peak expiratory flow rate (PEFR)

Baseline PEFR and PEFR did not differ significantly between groups and did not change during the study.

Physicians global evaluations (subjective rating)

The combination group had significantly better mean scores compared with the other two groups on days 15 and 29.

Symptom scores

COPD symptom scores did not change and did not differ between treatment groups.

Addition of steroid medication

3.8% patients – combination group

6.1% patients – Ipratropium group

	<p>10.4% patients – Albuterol group</p> <p>Addition of concomitant respiratory medication</p> <p>No significant difference between groups in use of concomitant respiratory medication.</p> <p>Adverse events (drug related)</p> <p>10.4% combination</p> <p>12.3% Ipratropium</p> <p>11.6% Albuterol</p> <p>Conclusion</p> <p>Combination of Ipratropium and Albuterol elicited statistically greater bronchodilators response (peak FEV and FVC) compared with either agent alone.</p>
SIGN Quality Rating	+ (Blinded double critical appraisal)
Hierarchy of Evidence Grading	1b
NCC CC ID	182

Author / Title / Reference / Yr	ZuWallack, R. L., MAHLER, D. A., Reilly, D., Church, N., Emmett, A., Rickard, K., & Knobil, K. 2001, "Salmeterol plus theophylline combination therapy in the treatment of COPD", <i>Chest</i> , vol. 119, no. 6, pp. 1661-1670. Ref ID: 1118
N=	N= 943 Location=US Sites – 74 Duration – 12 weeks
Research Design	Randomised, double-blind, double-dummy parallel group trial
Aim	To compare the efficacy and safety of salmeterol plus theophylline vs either agent alone in COPD
Operational Definition	FEV1 >0.7l and <65% predicted normal and FEV1/FVC ratio of <70%.
Population	<p>COPD due to chronic bronchitis or emphysema, >45 yrs old.</p> <p>Exclusion:</p> <p>History of asthma, daily continuous oxygen requirement, recent viral or bacterial pulmonary infection, congestive heart failure or other clinically active diseases.</p>
Intervention	<p>Salmeterol 42ug b.i.d. via metered dose inhaler (MDI) plus oral sustained-release theophylline twice daily</p> <p><i>(Ipratropium not permitted. No changes in regular COPD medication permitted. Stable doses of inhaled corticosteroids and/or oral corticosteroid doses (<10mg/d of prednisone or equivalent) were allowed)</i></p>
Comparison	<p>Salmeterol, 42ug b.i.d. via MDI or</p> <p>Oral sustained-release theophylline twice daily</p> <p><i>(Ipratropium not permitted. No changes in regular COPD medication permitted.. Stable doses of inhaled corticosteroids and/or oral corticosteroid doses (<10mg/d of prednisone or equivalent) were allowed)</i></p>

Outcome	FEV1, dyspnoea, using BDI and TDI, HRQOL assessed by CRDQ, satisfaction with treatment, peak expiratory flow (PEF ₁), daily COPD symptoms and albuterol use (rescue medication) on diary cards, exacerbations (could be treated with oral/parenteral corticosteroids for <14 days), adverse events																																							
Characteristics		Salmeterol/theophylline combination (n = 313)	Salmeterol (n = 310)	Theophylline (n = 315)																																				
	Age, yr	65.2	64.4	64.7																																				
	Male/female %	67/33	64/36	71/29																																				
	Pack years smoked	65.6 (1.8)	62.5 (1.5)	62.6 (1.6)																																				
	Treatment groups were balanced at baseline with respect to demographics and COPD history.																																							
Results	<p>Disposition and demographics 86% (803/938) of the patients completed the study. Common reason for withdrawal was adverse events, affecting 70 patients SALM +THEO group (6%) 19 patients SALM group (8%) 25 patients THEO group (8%) 26 patients. Medication compliance rates, as recorded by patients and by pill counts, were high (>90%)</p> <p>Pulmonary function</p> <table border="1"> <thead> <tr> <th>Variables</th> <th>Salmeterol/theophylline group (n = 300)</th> <th>Salmeterol group (n = 302)</th> <th>Theophylline group (n = 308)</th> </tr> </thead> <tbody> <tr> <td>Pre-dose FEV1</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Week 4</td> <td>+ 0.18 (0.01)</td> <td>+ 0.09 (0.02)</td> <td>+0.07 (0.01)</td> </tr> <tr> <td>week 8</td> <td>+0.17 (0.02)</td> <td>+ 0.08 (0.02)</td> <td>+ 0.07 (0.02)</td> </tr> <tr> <td>week 12</td> <td>+0.16 (0.02)</td> <td>+ 0.07 (0.02)</td> <td>+ 0.05 (0.02)</td> </tr> <tr> <td>Pre-dose FVC</td> <td></td> <td></td> <td></td> </tr> <tr> <td>week 4</td> <td>+0.30 (0.03)</td> <td>+0.15 (0.03)</td> <td>+0.11 (0.03)</td> </tr> <tr> <td>week 8</td> <td>+0.26 (0.03)</td> <td>+ 0.14 (0.03)</td> <td>+ 0.07 (0.03)</td> </tr> <tr> <td>week 12</td> <td>+0.24 (0.03)</td> <td>+ 0.10 (0.03)</td> <td>+0.04 (0.03)</td> </tr> </tbody> </table> <p>Pre-dose FEV1 and FVC Mean pre-dose FEV1 and FVC values significantly improved compared with baseline in both the SALM + THEO group and the SALM group at week 4, week 8 and week 12 (p<0.001). The same was true for the THEO group (p<0.021), with the exception of the pre-dose FVC assessment at week 12. The SALM + THEO group experienced significantly greater improvement in FEV1 and FVC than either the SALM group or the</p>				Variables	Salmeterol/theophylline group (n = 300)	Salmeterol group (n = 302)	Theophylline group (n = 308)	Pre-dose FEV1				Week 4	+ 0.18 (0.01)	+ 0.09 (0.02)	+0.07 (0.01)	week 8	+0.17 (0.02)	+ 0.08 (0.02)	+ 0.07 (0.02)	week 12	+0.16 (0.02)	+ 0.07 (0.02)	+ 0.05 (0.02)	Pre-dose FVC				week 4	+0.30 (0.03)	+0.15 (0.03)	+0.11 (0.03)	week 8	+0.26 (0.03)	+ 0.14 (0.03)	+ 0.07 (0.03)	week 12	+0.24 (0.03)	+ 0.10 (0.03)	+0.04 (0.03)
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THEO group (p<0.02)

Serial pulmonary function testing administered immediately pre-dose and at 0.5, 1, 2, 4, 6, 8, 10 and 12 h post-dose.

SALM + THEO group experienced significantly greater improvement at most time points compared with the SALM group or the THEO group (p<0.045)

The SALM group experienced significantly greater improvement compared with the THEO group in FEV1 and FVC during the first several hours postdose, most notably on day 1 (p<0.046)

The rank order of improvement (SALM + THEO > SALM > THEO) was similar in the reversible and nonreversible patients.

Evaluations of the FEV1 AUC showed that the SALM + THEO group experienced significantly greater improvement compared with the SALM group or the THEO group overall (all patients) and also for the subgroups of reversible and non reversible patients on day 1 and week 12 (p<0.002).

On day 1, the SALM group experienced significantly greater improvement compared with the THEO group overall and in the reversible patients (P<0.011)

There was no difference between the SALM group and the THEO group at week 12.

Other efficacy measures and COPD exacerbations

SALM + THEO group experienced significantly greater improvements in dyspnoea (TDI scores), albuterol-free days, and PEF, and required significantly fewer supplemental albuterol treatments than either the SALM group or the THEO group (p<0.08).

The SALM + THEO group experienced significantly more symptom-free days (p = 0.023) compared with the THEO group.

COPD exacerbations were experienced by significantly fewer patients in the SALM + THEO group (40 patients, 48 exacerbations) compared with the THEO group (62 patients, 96 exacerbations; p = 0.023), but not the SALM group (56 patients, 71 exacerbations; p = 0.076)

HRQOL and satisfaction with treatment

During the study, each treatment group experienced significant improvements compared with baseline in overall CRDQ scores.

The mean overall change from baseline in the SALM + THEO group (+11.2 points) was clinically meaningful (>10 points) and was significantly greater (p<0.019) at week 4 compared with the SALM group and the THEO group

At week 12, mean improvements in overall CRDQ scores were +12.7 points in the SALM + THEO group, +7.6 points in the SALM group, and +8.6 points in the THEO group.

A significantly higher percentage of patients in the SALM + THEO group (52 to 54%) experienced a clinically important improvement overall compared with the SALM group (36 to 45%) or the THEO group (31 to 42%) at week 4 and week 12 (p<0.014)

Improvement in pulmonary function were contrasted with improvements in HRQOL and TDI scores and found to be positively, but weakly correlated (r = 0.2 and r = 0.11 for FEV1 AUC and FVC vs HRQOL respectively and r = 0.19 and r = 0.14 for FEV1AUC and FVC vs TDI respectively)

SALM + THEO treatment was rated as providing significantly greater overall satisfaction with treatment compared with the THEO group at all time points (p<0.012) and compared with the SALM group at week 8 and week 12 (p<0.041)

SALM treatment provided significantly greater satisfaction with treatment with respect to side effects than either treatment involving theophylline (p<0.028)

	<p>Adverse events The proportion of patients reporting adverse events was not significantly different among treatment groups; however, the proportion of patients reporting adverse events that were judged to be related to study drug was significantly higher in both of the groups that received theophylline compared with the SALM group, most notably for GI events (p<0.042) Drug related cardiovascular events were reported relatively rarely (1-4% overall) and were similar among treatment groups. Serious adverse events were reported by 12 patients (4%) in the SALM + THEO group, 18 patients (6%) in the SALM group, and 16 patients (5%) in the THEO group.</p> <p>Cardiovascular Effects Mean heart rate significantly (p<0.004) increased relative to baseline for all patients during the theophylline titration period. Once randomised to study treatment, mean heart rates returned to baseline levels in the SALM group, but remained significantly elevated relative to baseline in both groups receiving theophylline.</p> <p>Conclusion Combination treatment with salmeterol plus theophylline consistently provided significantly greater improvements compared with either treatment alone in pulmonary function and significantly greater reduction in dyspnoea and albuterol use. Furthermore, combination treatment resulted in significantly fewer COPD exacerbations compared with theophylline and significantly greater improvements in HRQOL and patients' satisfaction with treatment. However, patients in the groups receiving theophylline experienced a higher frequency of GI side effects compared with those receiving salmeterol alone.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	1118

Author / Title / Reference / Yr	Bellia, V., Foresi, A., Bianco, S., Grassi, V., Olivieri, D., Bensi, G., & Volonte, M. 2002, "Efficacy and safety of oxitropium bromide, Theophylline and their combination in COPD patients: a double-blind, randomized, multicentre study (BREATH Trial)", <i>Respiratory Medicine</i> , vol. 96, no. 11, pp. 881-889. Ref ID: 1264
N=	N= 236 Location = Italy Sites – 29 Duration – 8 weeks
Research Design	Randomised, double-blind, double-dummy parallel group trial
Aim	To compare the efficacy and safety of inhaled oxitropium, theophylline or their combination in patients with mild-to-severe COPD.
Operational Definition	American Thoracic Society criteria FEV1 < 70% predicted.
Population	Clinical history of COPD as defined by ATS, were current or ex-smokers, between 35 and 80 yrs of age and baseline FEV1 <70% predicted

	<p>Exclusion: Patients with daily PEFr variability >20% and a change in FEV1 after 200ug Fenoterol >20% predicted value and total lung capacity >70% predicted, acute airways infection during preceding 4 weeks, blood eosinophilia > 8%, history of asthma, allergic rhinitis, cystic fibrosis and any atopic disease, peptic ulcer and liver, kidney or heart failure.</p>																																														
Intervention	<p>Inhaled oxitropium bromide 200ug b.i.d. plus sustained-release capsules of theophylline 300mg b.i.d. (2 puffs + 1 capsule in morning and evening) <i>(No concomitant bronchodilator medication permitted. Rescue medication of inhaled short acting B2-agonists permitted)</i></p>																																														
Comparison	<p>Placebo of oxitropium bromide plus sustained-release capsules of theophylline 300 mg b.i.d. (2 puffs + 1 capsule morning and evening) or Inhaled oxitropium bromide 200ug b.i.d. plus theophylline placebo capsules.(2 puffs + 1 capsule morning and evening) <i>(No concomitant bronchodilator medication permitted. Rescue medication of inhaled short acting B2-agonists permitted)</i></p>																																														
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Change at week 4 (n)	0.13 ± 0.05 (68)	0.05 ± 0.05 (75)	0.04 ± 0.04 (77)
Change at week 8 (n)	0.12 ± 0.07 (64)	0.05 ± 0.05 (71)	0.01 ± 0.05 (72)

Baseline FEV1 and FVC values in the three treatment groups were not different.

Although FEV1 and FVC values increased in all groups at weeks 4-8 no statistically significant differences between groups was observed.

Morning and evening baseline pre-dosing PEFr showed very little change at week 8 in all three treatment groups. In contrast, the morning post-dosing PEFr markedly increased in all three groups, particularly in the combination group; however, no statistically significant difference was observed between treatment groups for either morning or evening post-dosing PEFr change.

Symptoms and use of rescue bronchodilators

At baseline, symptoms scores for cough and dyspnoea in the three treatment groups were similar.

Decreased symptom intensity for cough frequency, cough intensity and dyspnoea were observed in the majority of patients in all three groups; however, no significant differences were observed between groups.

Quality of life

Bellia (2002) - RCT (n = 236 subjects – 8 weeks)

Total SGRQ score decreased in all groups (oxitropium/Theophylline combination, oxitropium alone and Theophylline alone) and the change was statistically significant compared with baseline (p<0.002)

Oxitropium + Theophylline p<0.0015

Theophylline p<0.001

Oxitropium p<0.0001

Decrease in total score reached the level of “clinical significance” only in patients treated with both oxitropium whether alone (4 ± 1.1 units) or in combination with Theophylline (4.7 ± 1.1 units). The decrease was mainly due to changes in activity and impact scores.

No significant differences between treatments were observed.

Safety

73 patients reported or exhibited a total of 135 events.

The most frequent adverse events were: epigastric pain in oxitropium + Theophylline group and COPD exacerbation in Theophylline group and oxitropium group.

The proportion of patients reporting treatment-related adverse events (p<0.02) and gastrointestinal treatment-related adverse events (p<0.04) in the Theophylline group was significantly greater than that found in oxitropium + Theophylline and oxitropium group.

Conclusion

In COPD patients, inhaled oxitropium bromide alone was associated with an improvement in PEFr and symptoms in patients with COPD that was not substantially difference from that of oral Theophylline alone or of the combination of both drugs; however, oxitropium bromide alone or in combination with Theophylline provided a better improvement in the quality of life than Theophylline alone as well as a better safety profile.

SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1264

Author / Title / Reference / Yr	Friedman, M., Serby, C. W., Menjoge, S. S., Wilson, J. D., Hilleman, D. E., & Witek, T. J., Jr. 1999, "Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD", <i>Chest</i> , vol. 115, no. 3, pp. 635-641. Ref ID: 1720 (combined results of ref 182 and ref 830) – only additional results presented				
N=	N= 1067 Location= US Sites – 24 Duration – 12 weeks				
Research Design	2 Prospective, double-blind, parallel group trials.				
Aim	To examine whether long-term administration of combined albuterol and ipratropium delivered in one inhalation aerosol would results in greater bronchodilation in patients with COPD than the use of either agent alone.				
Operational Definition	FEV \leq 65% of predicted normal and FEV1 \leq 70% FVC				
Population	<p>Inclusion Stable COPD > 40 years old, smoking history of more than 10 pack years and regularly using at least two prescribed therapeutic agents for control of COPD.</p> <p>Exclusion: History of asthma, allergic rhinitis or atopy, or with total blood eosinophil count above 500/mm³ Patients who required more than 10 mg of oral prednisone daily within a month before entry into the study</p>				
Intervention	Ipratropium bromide 42 μ g plus albuterol 200 μ g four times daily (two extra doses per day were permitted to control symptoms) (<i>Patients on stable dose of inhaled corticosteroids and/or theophylline could continue treatment</i>) Metered dose inhaler				
Comparison	Ipratropium bromide – dose 42ug four times daily Albuterol – dose 200ug four times daily Metered dose inhaler (<i>Patients on stable dose of inhaled corticosteroids and/or theophylline could continue treatment</i>)				
Outcome	Exacerbations, hospitalisation, corticosteroid use				
Characteristics		Ipratropium + albuterol	Ipratropium	Albuterol	Overall

	Randomised and treated	358	362	347	1067
	Age, yr (mean)	64.1	64	64.6	64.2
	Age, yr (range)	40-88	42-88	40-82	40-88
	Sex male	257	249	233	739
	Sex female	101	113	114	328
	FEV1 L mean	0.96	0.93	0.95	0.951
	FEV1 L range	0.25-2.34	0.23-2.78	0.32-2.43	0.23-2.78
	% pred FEV1 mean	35.1%	34.6	35.6	35.1
	% pred FEV1 range	10.4-76.2%	7.6-73.2	11.3-74.1	7.6-76.2
	FEV1/FVC mean	44%	44%	44%	44
	FEV1/FVC range	19-69%	19-69%	20-93%	19-93%
Results	Outcomes related to disease exacerbation				
		Albuterol	Ipratropium	Albuterol plus ipratropium	
	No of patients	347	362	358	
	No (%) of patients with exacerbation	62 (18) *	45 (12)	44 (12)	
	No of days per exacerbation				
	Mean	12.4	11.2	12.6	
	Median	8.5	9	9.5	
	Range	2-52	3-42	3-64	
	Total no of patient-days of exacerbation	770 *	504	554	
	No of hospitalisations due to exacerbation	11	3	5	
Hospital length of stay, days					

	No of patients adding or increasing doses of corticosteroids	42	32	32
	No of patient days of increased or added corticosteroid use	222 *	171	162
	No of patients adding or changing antibiotics	71	53	55
	No of patient days of changed or added antibiotic use	429 *	281	304
<p>*p<0.05 albuterol alone vs ipratropium alone vs albuterol plus ipratropium Compared with the other two treatment arms, patients receiving albuterol alone experienced a significantly increased frequency of COPD exacerbations (18%) and patient days of exacerbations (770 days) during the 85 day follow-up. The total days of exacerbation were similar in the two treatment arms containing ipratropium (504 days vs 554 days, respectively) compared with a significantly greater incidence of exacerbation (770 days) in the albuterol alone (p<0.05) No significant difference between treatment groups in exacerbation duration. Increased frequency of exacerbations in the albuterol arm was associated with a statistically significant increase in the number of total hospital days and greater corticosteroid and antibiotic use compared with the other two treatment arms (p<0.05) There was a significant increase in the total number of hospital days for albuterol alone (103 days) compared to either ipratropium alone (20 days) or ipratropium plus albuterol (46 days) Conclusion Long-term use of ipratropium alone or the combination of ipratropium plus albuterol is associated with fewer exacerbations of COPD than the use of albuterol alone.</p>				
SIGN Quality Rating	+			
Hierarchy of Evidence Grading	1b			
NCC CC ID	1720			

Author / Title / Reference / Yr	Nishimura, K., Koyama, H., Ikeda, A., Sugiura, N., Kawakatsu, K., & IZUMI, T. 1995, "The additive effect of theophylline on a high-dose combination of inhaled salbutamol and ipratropium bromide in stable COPD", <i>Chest.</i> , vol. 107, no. 3, pp. 718-723.
N=	N= 24 Location = Japan Sites – 1 Duration – 4 weeks

Research Design	Randomised double blind, placebo controlled crossover trial																				
Aim	To determine the additive effect of oral theophylline in patients with stable COPD who received both inhaled salbutamol 400ug and ipratropium bromide 80ug four times daily administered with metered dose inhaler																				
Operational Definition	FEV1 <80%, FEV1/FVC <70% predicted.																				
Population	Stable COPD, age >55 yrs, history of smoking of more than 20 pack years, chest radiograph showing hyperinflation with or without vascular deficiency pattern suggestive of pulmonary emphysema, FEV1/FVC <70% and FEV1 <80% predicted. Exclusion: History suggestive of asthma, heart disease, or any other illness. Patients treated with inhaled or systemic steroids in the preceding 3 weeks.																				
Intervention	Salbutamol 400ug and ipratropium 80ug daily dose using MDI + theophylline (serum concentration more than 10ug/ml) <i>(Use of bronchodilators not permitted)</i>																				
Comparison	Salbutamol 400ug and ipratropium 80ug daily dose using MDI + placebo <i>(Use of bronchodilators not permitted)</i>																				
Outcome	FEV1, FVC, PEFr, symptoms																				
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Results	<p>FEV1 Without inhalation of bronchodilators, FEV1 was 0.93 ± 0.42L during the placebo period and 1.00 ± 0.43L (significantly different from placebo, $p < 0.01$) during the theophylline period. At 15 and 60 minutes after inhalation of salbutamol, 400ug, and ipratropium bromide 80ug, the FEV1 with placebo was 1.12 ± 0.43L and 1.14 ± 0.46L respectively, and the FEV1 with theophylline was 1.18 ± 0.45L ($p < 0.01$) and 1.20 ± 0.47 L ($p < 0.01$), respectively. The FVC was not significantly different between the placebo and theophylline periods before and 15 and 60 minutes after the inhalation of the bronchodilating agents.</p> <p>PEFR Both preinhalation and postinhalation values of daily PEFr were significantly higher during the theophylline period than during the placebo period ($p < 0.01$)</p> <p>Symptoms No significant alteration of cough, sputum, wheezing, shortness of breath was observed throughout the different phases of treatment</p> <p>Responder vs non responder</p>																				

	<p>At the end of the study period, 15 patients did not recognise any symptomatic differences during the two crossover period with active or placebo administration (subjective nonresponders)</p> <p>Nine patients reported symptomatic improvement during one of the two treatment periods.</p> <p>One of nine patients preferred the placebo periods and was therefore a subjective non responder. The other eight patients were classified as subjective responders.</p> <p>Adverse events</p> <p>Sixteen patients (67%) complained of gastrointestinal side effects while receiving theophylline and 10 patients (42%) reported similar effects during placebo administration.</p> <p>Conclusion</p> <p>Theophylline has a small bronchodilating effect but does not improve the symptoms of patients with stable COPD.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1722

Author / Title / Reference / Yr	Calverley, P., Pauwels, R., Vestbo, J., Jones, P., Pride, N., Gulsvik, A., Anderson, J., & Maden, C. 2003, "Combined Salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: A randomised controlled trial", <i>Lancet</i> , vol. 361, no. 9356, pp. 449-456. Ref ID: 1702
N=	N= 1465 Location = 25 countries Sites – 196 hospitals Duration – 12 months
Research Design	Randomised double blind, placebo controlled parallel group trial
Aim	To assess whether long-acting B2-agonists and inhaled corticosteroids in combination will result in treatment effects that are better than those associated with either drug alone.
Operational Definition	Baseline FEV1 25-70% predicted
Population	<p>COPD patients, baseline FEV1 before bronchodilation 25-70% predicted, increase of less than 10% predicted FEV1 30 min after Salbutamol, prebronchodilators FEV1/FVC 70% or less. History of at least 10 pack years of smoking, chronic bronchitis, at least one episode of acute COPD symptom exacerbation per year in previous 13 years, at least one exacerbation in year immediately before trial entry.</p> <p>Exclusion:</p> <p>Respiratory disorders other than COPD, requirement for regular oxygen treatment, received systemic corticosteroids, high doses of inhaled corticosteroids (>1000ug daily beclamethason dipropionate, budesonide, or flunisolide or > 500ug daily fluticasone), or antibiotics in 4 weeks before the 2 week run-in period before the trial began.</p>
Intervention	Salmeterol and fluticasone combination (50/500ug twice daily) n = 358

	<i>(Anticholinergics, mucolytics and Theophylline use permitted. Salbutamol was allowed as rescue medication. Use of corticosteroids and bronchodilators not permitted)</i>																																		
Comparison	1) Salmeterol 50ug twice daily n = 372 2) Fluticasone 50ug twice daily n = 374 3) Placebo n = 361 <i>(Anticholinergics, Mucolytics and Theophylline use permitted. Salbutamol was allowed as rescue medication. Use of corticosteroids and bronchodilators not permitted)</i>																																		
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Results	<p>Pre-treatment FEV1 The three active treatments increased pre-treatment FEV1 significantly compared with placebo (salmeterol/fluticasone p<0.0001; Salmeterol p<0.0001; Fluticasone p = 0.0063) This improvements was evident by week 2 and was sustained throughout treatment Rise in FEV1 associated with combination therapy was significantly greater than with either of its components separately. By week 52, pre-treatment FEV1 in the combination group had increased by 10% compared with 2% in both the Salmeterol and Fluticasone group, and had fallen by 3 % in the placebo group.</p> <p>Number of exacerbations Compared with placebo, all active treatments significantly reduced the number of exacerbations per patient per year and the number of exacerbations that needed treatment with oral corticosteroids. The rate of exacerbations fell by 25% in the combination group (p<0.0001) and by 20% (p = 0.0027) and 19% (p = 0.0033) in the Salmeterol and Fluticasone groups respectively compared with placebo. The effect was more pronounced in patients with a baseline FEV1 of <50% predicted who showed a 30% with the combination compared with placebo, as against a 10% reduction in patients who had a baseline FEV1 that was greater than 50% of that predicted.</p>																																		

	<p>Acute episodes of symptom exacerbation that required oral corticosteroids were reduced by 39% in the combination group ($p < 0.0001$), 29% in the Salmeterol group ($p = 0.0003$) and 34% in the Fluticasone group ($p = 0.0001$) compared with placebo.</p> <p>Symptoms Combination treatment significantly reduced breathlessness and the use of relief medication compared with placebo, Salmeterol and Fluticasone. Median number of days without rescue medications was for placebo 0% (range 0-100%), Salmeterol 3% (0-100%), Fluticasone 2% (0-100%) and combination 14% (0-100%) ($p < 0.0001$ vs. placebo, $p = 0.004$ vs. Salmeterol, $p = 0.0003$ vs. Fluticasone) The number of night-time awakenings fell significantly in the combination groups, compare with placebo and Salmeterol, but not with Fluticasone. Cough only improved significantly in the combination group.</p> <p>Health Status Only the combination group showed a clinically significant improvement in health status questionnaire score by week 52.</p> <p>Adverse events All treatments were well tolerated, with no difference between groups in the number of patients reporting an adverse event during treatment (78-81% across groups)</p> <p>Conclusion Fluticasone and Salmeterol combination treatment produced better control of symptoms and lung function, with no greater risk of side effects than that with use of either component alone.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	1702

Author / Title / Reference / Yr	Szafranski, W., Cukier, A., Ramirez, A., Menga, G., Sansores, R., Nahabedian, S., Peterson, S., & Olsson, H. 2003, "Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease", <i>European Respiratory Journal</i> , vol. 21, no. 1, pp. 74-81. Ref ID: 1698
N=	N= 812 Location = 11 countries (Denmark, Finland, UK, Italy, South Africa, Spain, Poland, Brazil, Mexico, Argentina, Sweden) Duration – 12 months
Research Design	Randomised double blind, placebo controlled parallel group trial
Aim	To evaluate the efficacy and safety of budesonide/formoterol in a single inhaler compared with placebo and both components separately in patients with COPD.
Operational Definition	FEV1/FVC <70% and FEV1 <50% predicted normal

Population	Adults with moderate to severe COPD, outpatients >40 yrs, COPD symptoms for > 2 years, >10 pack-yrs smoking history, FEV1/FVC <70% and FEV1 <50% predicted normal, total symptom score >2 per day for at least 7 days of run-in period, documented use of short-acting inhaled bronchodilators for reliever medication, >1 severe COPD exacerbation within 2-12 months before first clinic visit Exclusion: History of asthma and/or seasonal allergic rhinitis before the age of 40, any relevant cardiovascular disorders, using B-blocking agents, current respiratory tract disorders other than COPD or any other significant diseases or disorders which may have put them at risk or which may have influenced the results of the study, a requirement for regular use of oxygen therapy or an exacerbation during run-in.																																								
Intervention	Budesonide 320ug /formoterol 9ug twice daily (Terbutaline 0.5mg per inhalation was allowed as rescue medication)																																								
Comparison	1) Budesonide 400ug twice daily 2) Formoterol 9ug twice daily (Terbutaline 0.5mg per inhalation was allowed as rescue medication)																																								
Outcome	Exacerbations, hospitalisations, daily diary cards to monitor symptoms, use of rescue medication, use of other COPD medication and PEF. Pulmonary function assessed at each visit. SGRQ Adverse events																																								
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Results	Severe Exacerbations Mean exacerbations rates per patient per year Budesonide/formoterol – 1.42 Budesonide – 1.59 Formoterol - 1.84																																								

Placebo – 1.87

Budesonide/formoterol significantly reduced the mean exacerbation rate compared with placebo and formoterol $p < 0.001$

Rate of oral steroid courses associated with exacerbations

Budesonide/formoterol – 0.74

Budesonide – 0.76

Formoterol – 1.04

Placebo – 1.07

Compared with placebo, both budesonide/formoterol ($p = 0.027$) and budesonide ($p = 0.045$) reduced the number of oral steroid courses used in association with exacerbations

Budesonide/formoterol also significantly reduced the number of oral steroid courses compared with formoterol ($p = 0.03$).

Mild Exacerbations

All active treatment arms reduced mild exacerbations compared with placebo

Budesonide/formoterol – by 62%

Budesonide – by 41%

Formoterol – by 55%

Budesonide/formoterol reduced mild exacerbations by 35% compared with budesonide ($p = 0.022$) and by 15% compared with formoterol ($p = 0.043$)

Lung function

FEV1

All active treatment increased FEV1 compared with placebo

Budesonide/formoterol also increased FEV1 compared with budesonide

Improvements in FEV1 were sustained with budesonide/formoterol throughout the study period compared with budesonide and placebo.

FVC

All active treatments improved FVC compared with placebo

Budesonide/formoterol – by 9% ($p < 0.001$)

Budesonide – by 4% ($p < 0.05$)

Formoterol – by 11% ($p < 0.001$)

Peak expiratory flow

Budesonide/formoterol improved and maintained morning and evening PEF compared with placebo, budesonide and formoterol alone ($p < 0.001$)

Symptoms

Budesonide/formoterol significantly reduced all symptom scores within the first week of treatment compared with budesonide, formoterol and placebo

This significant effect was sustained for 12 months for budesonide/formoterol compared with placebo, budesonide and formoterol

	<p>regarding the total score and awakenings. Budesonide/formoterol increased days free from shortness of breath by 12% compared with placebo (p<0.001) and awakening-free nights by 14% compared with placebo (p<0.001) Budesonide/formoterol reduced use of rescue medication by 1.3 and 0.7 inhalations per 24h compared with placebo and budesonide respectively (both p<0.001)</p> <p>Health-related quality of life A change in 4 points on the SGRQ from baseline is considered an important difference relevant to the patient. Mean reductions for SRGQ total score from baseline Budesonide/formoterol – 3.9 Budesonide – 1.9 Formoterol – 3.6 Placebo – 0.03 Compared with placebo, budesonide/formoterol significantly improved SGRQ total score (p = 0.009) and symptoms (p<0.001) and impact (p = 0.006)</p> <p>Safety The adverse event profile was similar in each group. Discontinuations due to COPD worsening were highest in the placebo group. The frequency of discontinuations due to other adverse events was similar in all groups.</p> <p>Conclusion Budesonide/formoterol reduced COPD exacerbations and provided early and sustained improvements in lung function and symptoms, together with improvements in health-related quality of life.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	1698

Author / Title / Reference / Yr	Mahler, D. A., Wire, P., Horstman, D., Chang, C.-N., Yates, J., Fischer, T., & Shah, T. 2002, "Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease", <i>American Journal of Respiratory & Critical Care Medicine</i> , vol. 166, no. 8, pp. 1084-1091. Ref ID: 1689
N=	N= 691 Location = US Sites – 65 Duration – 24 weeks
Research Design	Randomised double blind, placebo controlled parallel group trial
Aim	To assess the effectiveness and safety of fluticasone propionate/salmeterol combination and its individual components in the treatment of COPD

Operational Definition	FEV/FVC baseline of <70% and baseline FEV1 less than 65% of predicted but more than 0.70L																																																					
Population	<p>COPD patients, >40 yrs of age, current or former smokers with a 20 pack-year or more history. FEV/FVC baseline of <70% and baseline FEV1 less than 65% of predicted but more than 0.70L. Patients required to have daily cough productive of sputum for 3 months of the year for 2 consecutive years and dyspnoea.</p> <p>Exclusion: Current diagnosis of asthma, oral corticosteroid use within the past 6 weeks, abnormal clinically significant electrocardiogram, long-term oxygen therapy, moderate or severe exacerbation during run-in and any clinically significant medical disorder.</p>																																																					
Intervention	Fluticasone 500 mcg and salmeterol 50 mcg twice daily via metered dose inhaler <i>(Stable theophylline use permitted. Albuterol was allowed as rescue medication. Use of corticosteroids and bronchodilators not permitted)</i>																																																					
Comparison	<p>1) Fluticasone 500 mcg twice daily 2) Salmeterol 50 mcg twice daily 3) Placebo twice daily</p> <p><i>(Stable theophylline use permitted. Albuterol was allowed as rescue medication. Use of corticosteroids and bronchodilators not permitted)</i></p>																																																					
Outcome	Change in predose FEV1, change in 2 hour postdose FEV1, morning peak expiratory flow (PEF), supplemental albuterol use, dyspnoea assessed by the Transition Dyspnoea index (TID), the Chronic Bronchitis Symptom Questionnaire, exacerbations defined by treatment. Health status evaluated using the CRDQ, adverse events																																																					
Characteristics	<table border="1"> <thead> <tr> <th></th> <th>Placebo (n = 181)</th> <th>Salmeterol (50ug) (n = 160)</th> <th>Fluticasone 500ug (n = 168)</th> <th>Fluticasone/salmeterol combination (n = 165)</th> </tr> </thead> <tbody> <tr> <td>Male</td> <td>136</td> <td>103</td> <td>103</td> <td>103</td> </tr> <tr> <td>Female</td> <td>45</td> <td>57</td> <td>65</td> <td>62</td> </tr> <tr> <td>Age mean</td> <td>64</td> <td>63.5</td> <td>64.4</td> <td>61.9</td> </tr> <tr> <td>Age range</td> <td>44-90</td> <td>40-84</td> <td>42-82</td> <td>40-86</td> </tr> <tr> <td>Pack years smoked median</td> <td>60</td> <td>52.5</td> <td>54</td> <td>55</td> </tr> <tr> <td>Pack years smoked range</td> <td>20-165</td> <td>20-193</td> <td>20-200</td> <td>15-150</td> </tr> <tr> <td>Mean FEV1, ml</td> <td>1317</td> <td>1237</td> <td>1233</td> <td>1268</td> </tr> <tr> <td>mean FEV1, % predicted</td> <td>41</td> <td>40</td> <td>41</td> <td>41</td> </tr> <tr> <td>Mean FEV1/FVC</td> <td>0.49</td> <td>0.49</td> <td>0.48</td> <td>0.49</td> </tr> </tbody> </table>					Placebo (n = 181)	Salmeterol (50ug) (n = 160)	Fluticasone 500ug (n = 168)	Fluticasone/salmeterol combination (n = 165)	Male	136	103	103	103	Female	45	57	65	62	Age mean	64	63.5	64.4	61.9	Age range	44-90	40-84	42-82	40-86	Pack years smoked median	60	52.5	54	55	Pack years smoked range	20-165	20-193	20-200	15-150	Mean FEV1, ml	1317	1237	1233	1268	mean FEV1, % predicted	41	40	41	41	Mean FEV1/FVC	0.49	0.49	0.48	0.49
	Placebo (n = 181)	Salmeterol (50ug) (n = 160)	Fluticasone 500ug (n = 168)	Fluticasone/salmeterol combination (n = 165)																																																		
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	Demographic and baseline characteristics were similar across all treatment groups
Results	<p>Lung function</p> <p>Predose FEV1 A significantly greater increase in predose FEV1 at the endpoint was observed after treatment with combination therapy (156ml) compared with salmeterol (107 ml) $p = 0.012$ and placebo (-4ml) $p < 0.001$ Significantly greater increases in predose FEV1 were observed for treatment with combination compared with that for salmeterol beginning at week 1 (173 vs 127 ml $p = 0.032$) and at most other time points during the study A significantly greater increase in predose FEV1 was also observed for treatment with fluticasone vs placebo at the endpoint (109 vs -4ml respectively $p < 0.001$) as well as at all assessment points throughout the study, with the exception of week 8.</p> <p>Two hour post-dose FEV1 A significantly greater increase in 2 hour post dose FEV1 at the endpoint was observed after treatment with combination therapy (261 ml) compared with fluticasone (138ml, $p < 0.001$) and placebo (28ml, $p < 0.001$) Significantly greater increases in 2 hour postdose FEV1 were observed at Day 1 and throughout the study during treatment with combination therapy compared with fluticasone. Significantly greater increases in 2-hour postdose FEV1 were observed for the salmeterol group versus placebo (233 vs 28ml, respectively $p < 0.024$) at the endpoint and at all assessment points throughout the study.</p> <p>Response by reversibility Patients who demonstrated reversibility of airway obstruction with albuterol had slightly better improvements in predose FEV1, 2-hour postdose FEV1 and TDI with individual components as well as with combination treatment.</p> <p>Morning PEF rate Increases in morning PEF on Day2, approximately 24 hours after the initiation of treatment, were greater for combination treatment compared with fluticasone, salmeterol and placebo ($p < 0.005$) Greater increases in morning PEF were observed throughout the 24 week treatment period with combination treatment compared with fluticasone, salmeterol and placebo. The overall change from baseline in morning PEF with combination treatment (31.9L/min) was greater than the sum of the mean changes from baseline observed with the individual components, 12.9 and 16.8L/min for fluticasone ($p < 0.001$) and salmeterol ($p < 0.001$), respectively. Mean overall changes from baseline were also significantly greater for both fluticasone and salmeterol versus placebo ($p < 0.001$)</p> <p>Dyspnoea At the endpoint, the mean TDI score for treatment with combination drug (2.1) was greater than that after treatment with fluticasone (1.3, $p = 0.033$) and was significantly greater than that after treatment with salmeterol (0.9, $p < 0.001$) and placebo (0.4, $p < 0.001$) Significant differences in TDI scores were observed as early as Week 1 with combination treatment as compared with fluticasone, salmeterol and placebo. At the endpoint, TDI scores were significantly greater for fluticasone (1.3, $p = 0.002$), but not salmeterol, compared with placebo.</p>

	<p>Supplemental Albuterol Use Significant reductions in overall albuterol use (number of inhalations per day and percentage of days without albuterol use) were observed during treatment with combination compared with fluticasone and placebo. A significant reduction in overall albuterol use was also observed after treatment with salmeterol compared with placebo and with fluticasone compared with placebo. A significant increase in the overall percentage of nights with no awakenings requiring albuterol was observed for treatment with combination, fluticasone and salmeterol compared with placebo (p<0.001)</p> <p>Health Status At the endpoint, treatment with combination therapy resulted in a clinically important increase from baseline in mean overall CRDQ score (10) that was significantly greater compared with the placebo (5.0, p = 0.007) and fluticasone (4.8, p = 0.017) groups, but not with salmeterol (8.0) Clinically important increases in dyspnoea score (4.2), fatigue score (2.0) and physical summary score (6.1) were observed after treatment with combination. These increases were also statistically significant versus the fluticasone and placebo treatment groups (p<0.016)</p> <p>Safety A total of 515 (75%) of patients experienced at least one adverse event during the study. A greater percentage of patients in the fluticasone and the combination groups experienced candidiasis (mouth/throat) based on visual inspection compared with the placebo and salmeterol groups. Three deaths were not considered to be related to study drugs.</p> <p>Conclusion Combination treatment provided significantly greater improvements in predose and 2 hour postdose FEV1 as well as in morning PEF compared with individual components or placebo. Combination treatment significantly reduced the severity of dyspnea as measured using the TDI compared with salmeterol and placebo. There were significant reductions in albuterol use as a rescue medication with combination treatment compared with fluticasone and placebo Combination treatment resulted in significant increases in health status, as measured using the CRDQ compared with fluticasone and placebo.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	1689

Author / Title / Reference / Yr	Taylor, D. R., Buick, B., & Kinney, C. 1985, "The efficacy of orally administered theophylline, inhaled salbutamol, and a combination of the two as chronic therapy in the management of chronic bronchitis with reversible air-flow obstruction", <i>American Review of Respiratory Disease</i> , vol. 131, no. 5, pp. 747-751. Ref ID: 657
N=	N= 25. Location=UK. Sites – 1. Duration – 12 weeks.
Research Design	Randomised, double-blind, crossover controlled trial Efficacy of three study medications, salbutamol, theophylline and a combination of the two delivered by inhaler and tablets were compared after 3 weeks on each of the double-blind study medications during the crossover phase of the trial.
Aim	To assess the efficacy of bronchodilator therapy in the long-term management of patients with chronic bronchitis and varying degrees of reversible air-flow obstruction.
Operational Definition	Cough productive of mucoid sputum on most days for 3 months of 2 consecutive years and at least 10% improvement in FEV1 after inhalation of salbutamol.
Population	Chronic bronchitis with reversible airflow obstruction Exclusion: Patients with episodic attacks of wheeze, not associated with chest infection, or with history of atopy, and those with cardiac or hepatic dysfunction.
Intervention	Salbutamol via MDI (Ventolin) 200ug 4 times daily and sustained release theophylline tablets twice daily (Theolair SR) (Th/S)
Comparison	Salbutamol inhaler and placebo tablets (S/P) Theophylline tablets and placebo inhaler (Th/P) Placebo inhaler and placebo tablets (P/P)
Outcome	“Treatment failure” defined as need to administer additional therapy because of a noninfective relapse, FEV1, FVC, functional residual capacity (FRC), peak flow rate (PFR) and diary-recorded symptoms
Characteristics	21 males, 4 females Mean age 63 yrs *range 45-73 years) 2 non-smokers, 4 smokers and 19 ex-smokers. Mean pack years 43 ± 6 yrs (range 8 to 144) FEV1 15.4 to 78% predicted
Results	Treatment failure 24 out of the 100 treatment periods were “treatment failures” 9 occurred during P/P 8 during P/S 6 during Th/P 1 during Th/S

In each case, after appropriate treatment, the discontinued period was recommenced from the beginning and was completed in full without interruption.

Rescue medication

Thirteen patients required intervention with additional bronchodilator therapy during at least 1 of the 4 treatment periods because of significant symptomatic deterioration.

12 patients completed all 4 periods of treatment without requiring additional therapy.

No difference between these patients and the 13 who experience “treatment failures”.

Theophylline doses

Theophylline doses administered to individual patients ranged from 500 to 1400 mg/day and during the treatment periods, the plasma theophylline concentrations measured 1 to 3 h after tablet ingestion were

Th/P 13.1 ± 1.3 ug/ml (n = 19) and

Th/S 13.1 ± 1.1 ug/ml (n = 24)

		Placebo	Theophylline	Salbutamol	Theophylline
	Pretreatment	Placebo	Placebo	Placebo	Salbutamol
FEV1, L	1.15 ± 0.17	1.14 ± 0.17	1.27 ± 0.19	1.22 ± 0.16	1.38 ± 0.19
% predicted	36.8 ± 5.2	36.1 ± 4.9	40.4 ± 5.5	38.6 ± 4.7	44.1 ± 5.4
FVC, L	2.5 ± 0.23	2.55 ± 0.24	2.69 ± 0.24	2.74 ± 0.23	3.02 ± 0.25
% predicted	63.4 ± 7.1	58.9 ± 8.4	67.5 ± 6.8	67.1 ± 5.7	75.2 ± 6.6
FRC, L	4.8 ± 0.23	5.01 ± 0.36	4.9 ± 0.24	4.79 ± 0.37	4.7 ± 0.16
% predicted	147.1 ± 7.3	152.8 ± 9.8	150.3 ± 7.7	145.7 ± 9.7	144.4 ± 6.4
RV, L	3.88 ± 0.19	4.12 ± 0.38	3.80 ± 0.22	3.86 ± 0.33	3.64 ± 0.17
% predicted	187.9 ± 9.1	198 ± 15.4	184 ± 10.5	186.5 ± 14.4	176 ± 7.8
TLC	6.65 ± 0.23	7.01 ± 0.32	6.94 ± 0.22	6.82 ± 0.37	6.83 ± 0.20
% predicted	119.4 ± 6.1	124.2 ± 6.6	122.6 ± 5.7	113.6 ± 12	121.4 ± 5.3
RV/TLC %	58.3 ± 1.9	58.1 ± 3.2	54.6 ± 2.4	56.1 ± 3.1	53.2 ± 1.8
% predicted	155.8 ± 6.77	155 ± 9.4	145.9 ± 7.5	148.7 ± 7.5	142.2 ± 6.6

FEV1/FVC

Improvement in mean values for FEV1 (% predicted) compared with treatment P/P

Th/P 4.3%

P/S 2.5%

Th/S 8.0%

Improvement in mean values for FVC (% predicted) compared with treatment P/P

	<p>Th/P 8.6% P/S 8.2% Th/S 16.3%</p> <p>Compared with placebo, values for FEV1, FVC and RV/TLC were significantly improved during combined therapy. In addition, combined therapy was better than salbutamol alone for FEV1 and FVC. Theophylline alone resulted in small but significant change in FEV1, but in no other index of lung function. Salbutamol alone did not result in any significant improvement.</p> <p>Symptomatic relapse</p> <p>1 out of 25 patients experienced symptomatic relapse during 3 weeks of continuous treatment with combination therapy, compared with 6, 8 and 9 during treatment with theophylline alone, salbutamol alone and placebo, respectively. Using a ranking system based on "treatment failure" and daily PFR recordings, 13 patients were adjudged best receiving combined therapy, in contrast to only 6 using theophylline, 4 receiving salbutamol and 2 receiving placebo.</p> <p>Conclusion</p> <p>Combination therapy showed significant improvements in FEV1 and FVC compared with placebo. Such improvements were not seen with either agent alone.</p>
SIGN Quality Rating	- (Blinded double critical appraisal)
Hierarchy of Evidence Grading	1b
NCC CC ID	657

Author / Title / Reference / Yr	Karpel J, Kotch A, Zinny M et al. A comparison of inhaled ipratropium, oral theophylline plus inhaled beta agonist and the combination of all three in pts with COPD. Chest 1994 Vol. 154, No. 4.
N=	N=48 Duration=4 separate days Location=USA Pts entered into the study received four separate drug regimens on four non-consecutive days within a 45-day period.
Research Design	Double blind, placebo controlled study
Aim	Purpose of the study was to compare the efficacy of ipratropium alone, oral theophylline plus an inhaled beta agonist, or the combination of ipratropium, beta agonist and theophylline in pts with stable COPD.
Operational Definition	Stable COPD as defined by ATS. Baseline FEV1 65% predicted or less
Population	Stable COPD (Asthma excluded)
Intervention and Comparisons	<ol style="list-style-type: none"> 1. Theophylline tablets (individual doses) followed by Inhaled albuterol (2 puffs via MDI) followed by Inhaled placebo (2 puffs via MDI) 2. Oral placebo followed by ipratropium (2 puffs via MDI; 36ug) followed by inhaled placebo

	<p>3. Oral theophylline, followed by albuterol, followed by ipratropium</p> <p>4. Oral placebo followed by two inhaled placebos</p>
Outcomes	Spirometry and heart rate were measured at 0, 30, 60 mins and hourly for 6 hrs.
Characteristics	<p>Concomitant medications – inhaled and short acting oral beta adrenergic medications, anticholinergics, inhaled steroids and were withheld for the 8h preceding each study and during testing. Long acting beta agonists were withheld for 24 h. Pts were included if they required less than 10mg/d of prednisone. For pts receiving alternate day steroids, the study was performed on the days that steroids were not taken. Cromolyn sodium was excluded. Mean age = 62yrs</p> <p>Sex= 54% male</p> <p>Ethnic origin=Not detailed</p> <p>Mean baseline FEV1 0.9L, range 0.32-1.56</p>
Results	<p>Efficacy</p> <p>There were no significant improvements with placebo.</p> <p>Mean peak FEV1 and area under the FEV1 time curve above baseline were compared among treatment groups:</p> <p>Ipratropium was significantly more effective than placebo (p=0.0001 and p=0.0078 respectively).</p> <p>Combination therapy with albuterol and theophylline was superior to ipratropium alone (p=0.0001 and p=0.0001 respectively).</p> <p>All three medications given together (Ipratropium, albuterol and theophylline) were more effective than the combination of albuterol and theophylline (p=0.0373 and p0.0289 respectively).</p> <p>FVC responses are similar to FEV1 responses.</p> <p>Median onset of action was 1h for ipratropium and 30 min for the combination of theophylline and albuterol and for the combination of all three agents.</p> <p>Heart Rate - Safety</p> <p>Theophylline and albuterol caused a greater increase in heart rate than did ipratropium alone (p=0.0001).</p> <p>The combination of theophylline, albuterol and ipratropium caused a greater increase in heart rate compared with ipratropium alone (p=0.0001).</p> <p>There were no significant difference in the peak heart rates between theophylline and albuterol regimen and the regimen that included all three agents (p=0.1329)</p> <p>Adverse Events</p> <p>There were no serious adverse events.</p>
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	189

Section 7.8 Delivery systems used to treat patients with stable COPD

N= 130 Literature search
N= 94 excluded from abstracts
N= 31 full papers ordered and of these;
N= 5 papers critically appraised
N= 26 papers excluded
N= 7 paper found on cross referencing

Author	Publication Date	ID	SIGN Grade	Hierarchy
Boe, J., Dennis, J. H., O'Driscoll, B. R., Bauer, T. T., Carone, M., Dautzenberg, B., Diot, P., Heslop, K., & Lannefors, L. 2001, "European Respiratory Society Guidelines on the use of nebulizers. 1", <i>Eur Respir J</i> , vol. 18, no. 1, pp. 228-242. Ref ID: 19264	2001	19264	++	IV
Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. <i>Health Technol Assess</i> 2001; 5 (26). Review E: bronchodilators for stable and acute COPD – hand-held inhalers versus nebulisers	2003	1374	++	1a
Ram (Cochrane)	2003	1375	++	1a
Cuvelier	2002	1428	+	1b
Eiser	2001	1429	+	1b
O'Driscoll	1992	1432	-	Non-randomised prospective study
Turner et al	1997	945	++	

Author / Title / Reference / Yr	Boe, J., Dennis, J. H., O'Driscoll, B. R., Bauer, T. T., Carone, M., Dautzenberg, B., Diot, P., Heslop, K., & Lannefors, L. 2001, "European Respiratory Society Guidelines on the use of nebulizers. 1", <i>Eur Respir J</i> , vol. 18, no. 1, pp. 228-242. Ref ID: 19264
Design	Guidelines
Aim	<ol style="list-style-type: none"> 1. To improve clinical practice 2. To enhance the safety and efficacy of nebulizer use 3. To serve as an educational and scientific resource for healthcare professionals 4. To stimulate future research y identifying areas of ignorance and uncertainty.
Operational Definition	<p>Nebulizer defined as a device that can convert a liquid into aerosol droplets suitable for pt inhalation. To avoid confusion between nebulisers and an expanding range of hand held metered dose inhalers, the guidelines discuss only nebulizer devices in which the end user must load the medication into the device prior to each treatment. Air jet nebulisers are the most widely used although ultrasonic nebulisers are becoming more common.</p> <p>The guidelines recognise the influence of all the components attached to the nebulizer that affect performance and include flow/pressure characteristics of the compressed air, connection tubing, patient interface including mouthpiece or facemask.</p>
Population	Guidelines cover heterogeneous respiratory population (as well as adults and paediatrics) hence only the findings relevant to an adult COPD population have been extracted for this evidence table.
Criteria used for grading of recommendations	<p>Evidence and recommendations have been graded in accordance with SIGN and the Agency for Health Care policy and Research (AHCPR) scoring system.</p> <p>Grade A – Requires at least one RCT as part of the body of literature of overall good quality and consistency, addressing the specific recommendation.</p> <p>Grade B requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendations.</p> <p>Grade C requires evidence from expert committee reports or opinions and or clinical experience of respected authorities (including opinions of the ERS Nebulizer Task Force). It indicates absence of directly applicable studies of good quality.</p>
Recommendations	<p>Choice of nebulizer system</p> <p>Although a facemask may theoretically deliver less medication to the lungs, two clinical studies (not referenced) have shown equivalence between facemasks and mouth pieces for bronchodilator effects, possibly due to the tendency of breathless pts to mouth breathe (Grade B).</p> <p>A facemask should ideally be avoided if a nebulised steroid is administered (to avoid steroid administration to the facial skin and eyes) (Grade C).</p> <p>It should also be avoided or sealed very tightly if anticholinergic agents are to be administered to patients with glaucoma (Grade C).</p> <p>How to select the optimal system for a given patient or usage</p> <p>It is recommended that a standard operating practice (SOP) be adopted for each nebulizer system in use. (Grade C).</p> <p>Delivery system in COPD</p> <p>COPD pts should ideally receive monitored oxygen therapy while using an air driven nebulizer system however shorter nebulization periods (<10 minutes) may make this less of an issue with future nebulizer systems.</p>

	<p>Theoretically a mouth piece may be better as it avoids nasal deposition of drugs, although no advantage has been found in two small clinical studies (not referenced) in stable asthma and COPD.</p> <p>A nebulizer system, which is known to be efficient, should be used (use CEN data). Facemasks or mouthpieces are probably equally effective (Grade B) but breathless pts may prefer facemasks (Grade B).</p> <p>Use of nebulised bronchodilator drugs in COPD</p> <p>Most indications for bronchodilator therapy are best managed by the use of a hand held inhaler device (including a spacer device if appropriate). (Grade A).</p> <p>Doses of salbutamol <1mg or ipratropium bromide >160 – 240 ug may be given more conveniently using a jet nebulizer device (Grade C).</p> <p>High dose therapy should only be considered for pts with severe airflow obstruction as defined in asthma and COPD guidelines (Grade C).</p> <p>Nebulized therapy may also be required for some adult pts who, after assessment, cannot use a hand held inhaler device, even with appropriate spacer attachments (Grade C).</p> <p>If nebulized therapy is thought to be inappropriate for individual pts with COPD, it is recommended that the pt should be referred for “inhaled therapy optimisation” (Grade C).</p> <p>Inhaled therapy optimisation protocol for pts with COPD</p> <p>It is recommended that pts should be referred for “inhaled therapy optimisation” rather than a “trial of home nebulizer”. Experience has shown that pts who have completed a protocol (itemised in the guidelines but not detailed here) 50% of such pts have expressed a preference for nebulized therapy and 50% expressed a preference for a hand held inhaler, usually at a higher dose than they had previously taken.</p> <p>Choice of device for home nebulizer therapy</p> <p>Pts should be allowed to choose whether they prefer a facemask or a mouth piece to administer their nebulized treatment, unless their therapy specifically requires a mouth piece (Grade C).</p>
AGREE Quality Rating	++
Hierarchy of Evidence Grading	<p>IV</p> <p>Although these guidelines have been graded as “IV” within the hierarchy of evidence it should be noted that the ERS commissioned a Task Force to review the scientific and clinical principles of nebulised therapy and to produce a set of guidelines (evidence-based whenever possible) for users of nebulised treatment in Europe.</p>
NCC CC ID	ID: 19264

Author / Title / Reference / Yr	Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. Health Technol Assess 2001; 5 (26). Review E: bronchodilators for stable and acute COPD – hand-held inhalers versus nebulisers
N=	N=13 RCTs. 3 RCTs looked at acute COPD, 1 RCT included asthma patients.
Research Design	Meta analysis
Aim	To compare bronchodilator drugs delivered by inhaler devices to nebulisers for the treatment of patients with acute and stable COPD
Operational Definition	Operational definition of COPD not provided
Population	Pts with chronic bronchitis (1 RCT), acute exacerbations of COPD (3 RCT), COPD (8 RCT)
Intervention	Bronchodilator administered via nebuliser
Comparison	Bronchodilator administered via hand-held inhaler
Outcome	Primary outcome - FEV1. Other outcomes not reported consistently across studies.
Characteristics	Table summarising characteristics of included studies present in paper; however, inclusion criteria not explicitly stated. Reasons for study exclusion were; mixed populaion of asthma, COPD, review articles, study design other than RCT, no direct comparison of interventions.
Results	Pulmonary Function Using FEV as primary outcome, no clinical benefit of using nebulised medication in addition to or as an alternative to a pMDI, with or without a spacer, or a DPI in stable COPD. Standardised mean difference (SMD) [95% CI] Nebuliser vs pMDI alone: -0.10 (95% CI, -0.39 to 0.20) Nebuliser vs pMDI + spacer: -0.02 (95% CI, -0.33 to 0.3) Nebuliser vs DPI: 0.15 (95% CI, -0.15 to 0.45) Combined 0.01 (95% CI, -0.17 to 0.18) Using typical group data of FEV1 0.8 litres and SD 0.3 litres, this equates to 3ml (95% CI ± 50ml) in favour of MDI. Less available data for measures of disease such as PEFr or symptom scores, but it also shows no benefit of nebulised medication over MDI; however, confidence intervals are wide.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
NCC CC ID	1374 (also summarised in 1373)
Studies Included	Berry et al., 1989, Gross et al., 1989, Ikeda et al., 1999, Jenkins et al., 1987, Shim & Williams, 1984, Allen et al., 1988, Hansen, 1989, Hansen et al ., 1994, Hansen & Andersen, 1995., Maguire et al., 1991, Turner et al., 1988

Author / Title / Reference / Yr	Ram FSF, Brocklebank DM, Muers M, Wright J, Jones PW. Pressurised metered-dose inhalers versus all other hand-held inhalers devices to deliver bronchodilators for chronic obstructive pulmonary disease.(Cochrane Review). <i>The Cochrane Library.Oxford:Update Software 2003;Issue 3</i> . Review completed 2001
N=	n = 3 RCTS (all crossover studies n =61 patients total)
Research Design	Cochrane Review
Aim	To determine the efficacy of pressurised metered dose inhalers (pMDI) compared with any other handheld inhaler device for the delivery of bronchodilators in non-acute COPD.
Operational Definition	Studies were considered in patients who fitted internationally accepted criteria for the definition of COPD (e.g. ATS, BTS, ERS guidelines). Definition of chronic airflow obstruction in the appropriate clinical setting of older (>30 years), usually (ex) smoking patients having an FEV1 <70% and FEV1/FVC <70% of predicted or were diagnosed by a (respiratory) physician as having COPD.
Population	COPD
Intervention	Studies were considered which described the use of pMDI (with or without spacer device)
Comparison	Any other hand-held inhaler for the delivery of the same bronchodilator Formgren 1994 (terbutaline administered via Turbuhaler) Iacono 2000 (ipratropium bromide administered via Respimat) Ikeda 1999 (salbutamol administered via Rotahaler)
Outcome	Primary Physiological lung function measurements / validated quality of life measures Secondary Symptom scores / use of additional relief medication / use of inhaled or oral steroid treatment / severity of disease / days of work / compliance / patient preference / side effects / systemic bioavailability / subsidiary physiological measures / acute exacerbations
Characteristics	Table summarising characteristics of included studies present in paper. Reasons for study exclusion given. Patient characteristics included smoking history, male/female ratio, baseline pulmonary function
Results	For the Turbuhaler vs pMDI (Formgren 1994) none of the reported outcome measures were significantly different. Absolute change from baseline 1) Forced Expiratory Volume Weighted mean difference (WMD) [fixed] [95% CI] = 0.000 [-0.064, 0.064] 2) FVC WMD [fixed] [95% CI] = 0.056 [-0.158, 0.271] 3) Residual Volume WMD [fixed] [95% CI] = 0.203 [-0.231, 0.637] 4) Sgaw WMD [fixed] [95% CI] = 0.034 [-0.062, 0.129] 5) Treatment Failures/Drop outs = Not estimable

	<p>6) Adverse Event = Not estimable For the Rotahaler vs pMDI (Ikeda 1999), none of the reported outcome measures were significantly different. Mean absolute value 1) FEV1 - WMD [fixed] [95% CI] = 0.031 [-0.190, 0.252] 2) AUC-FEV1 - WMD [fixed] [95% CI] = 6.863 [-7.449, 21.175] 3) FVC - WMD [fixed] [95% CI] = 0.050 [-0.239, 0.338] 4) Heart Rate - WMD [fixed] [95% CI] = 0.380 [-7.811, 8.572] 5) Systolic Pressure - WMD [fixed] [95% CI] = 2.600 [-3.975, 9.175] 6) Diastolic Pressure - WMD [fixed] [95% CI] = 0.022 [-3.155, 3.199] 7) Treatment Failures/Drop outs - Relative Risk [fixed] [95% CI] = Not estimable 8) Adverse Events - Relative Risk [fixed] [95% CI] = 0.33 [0.02, 7.32] The study using the Respimat vs pMDI (Iacono 2000) showed significant increases in FEV1 when compared with pMDI (difference in change from baseline 70ml, 95% CI 10, 130ml). The effect on change in FVC was of similar size; however, no differences observed for other reported outcomes. <u>Absolute change from baseline</u> 1) FEV1 - WMD [fixed] [95% CI] = 0.070 [0.015, 0.125] 2) FVC - WMD [fixed] [95% CI] = 0.100 [0.077, 0.123] 3) Heart rate - WMD [fixed] [95% CI] = 1.120 [-2.915, 5.275] 4) Adverse Events - Relative Risk [fixed] [95% CI] = 3.69 [0.82, 16.62]</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
NCC CC ID	1375
Studies Included	Formgren 1994, Iacono 2000, Ikeda 1999

Author / Title / Reference / Yr	Cuvelier A, Muir J-F, Benhamou D, Guerin J-C, Weitzenblum E, Zuck P, Delacenserie R, Taytard A, Philip-Joet F, Iacono P. Dry powder ipratropium bromide is as safe and effective as metered-dose inhaler formulation: A cumulative dose-response study in chronic obstructive disease patients
N=	N=39. Location=France. Site= home-based. Duration – 2 days.
Research Design	Prospective randomised 2-way crossover study
Aim	To compare the safety and efficacy of cumulative doses of ipratropium bromide administered from a pressured metered-dose inhaler (MDI) or from a breath-activated dry powder inhaler (DPI)
Operational Definition	Clinical diagnoses of COPD and;

	<p>be over 40 years old, have a smoking history of more than 10-pack years moderate to severe airway obstruction, with a baseline FEV₁ < 65% of predicted, an initial FEV₁ <70% of the forced vital capacity (FVC), and a \leq15% increase in FEV₁ above baseline 45 minutes after 80μg (ie, 4 puffs x 20μg/puff) of ipratropium bromide via MDI.</p>
Population	Clinical diagnoses of COPD (based on American Thoracic Society criteria)
Intervention	Dry powder inhaler crossover to metered dose inhaler n = 19
Comparison	Metered-dose inhaler crossover to dry powder inhaler n = 17
Outcome	Efficacy - FEV ₁ increase between baseline and 45 minutes from last dose (195 min)/ FVC increase between baseline and 45 min after last dose (195 min)/ the FEV ₁ increase at 230-280 min (determined as area under the curve for FEV ₁ increase from baseline divided by the number of hours), and the FEV ₁ and FVC values at each time point during study day.
Characteristics	<p>Average age 59.8 \pm 8.4 years (range 44-81 years) Mean duration COPD 12 \pm 8 yrs (range 0-36 y) All active smokers or ex-smokers No differences between 2 groups at inclusion</p>
Results	<p>Pulmonary function Both DPI and MDI produced significant improvement in pulmonary function With both formulations, 80-90% of bronchodilator response was obtained after first 2 doses of 20μg (cumulative doses of 20 and 40μg) ipratropium bromide. Subsequent additional doses did not improve pulmonary function. No significant differences between groups. FEV₁ absolute values – 5 to 230 min (L) = DPI 323 \pm 104; MDI 318 \pm 102) FEV₁ absolute values 230 to 380 min (L) = DPI 219 \pm 73; MDI 213 \pm 65) FEV₁ absolute changes – 5 to 230 min (L) = DPI 65 \pm 38; MDI 60 \pm 39) FEV₁ absolute changes 230 to 380 min (L) = DPI 55 \pm 35; MDI 51 \pm 39) FVC absolute values – 5 to 230 min (L) = DPI 615 \pm 142; MDI 600 \pm 153) FVC absolute values 230 to 380 min (L) = DPI 410 \pm 102; MDI 402 \pm 107) FVC absolute changes – 5 to 230 min (L) = DPI 110 \pm 68; MDI 100 \pm 71) FVC absolute changes 230 min to 380 (L) = DPI 88 \pm 60; MDI 86 \pm 81)</p> <p>Safety Rate and type of adverse effects were similar for both devices The number of reported adverse effects was low No severe adverse effects described</p> <p>Patient acceptability Handling of DPI considered easier than the MDI (p= 0.014), and the DPI was preferred to the MDI (p<0.001).</p>

	<p>Patient ease-of-use scores were 3.72 ± 0.45 for the DPI and 3.31 ± 0.71 for the MDI ($p= 0.014$) Patients preference scores were 3.17 ± 0.45 for the DPI, and 2.64 ± 0.68 for the MDI ($p<0.001$). Fifty-six percent of the patients considered the DPI easier to use than the MDI Conclusion Patients with stable COPD in this trial do not benefit from nebulised therapy compared with alternative therapy.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1428

Author / Title / Reference / Yr	Eiser N, Angus K, McHale S. The role of domiciliary nebulizers in managing patients with severe COPD. Respiratory Medicine 2001 95, 265 -274
N=	N= 19. Location=UK.
Research Design	Double blind, randomised crossover trial
Aim	<p>To determine whether in patients with severe COPD: bronchodilators produce greater effects when given via a nebulizer than when given in conventional doses via MDIs both in the laboratory and in the domiciliary setting; there is a significant placebo effect from receiving a nebulized aerosol acute bronchodilator responses of lung function, walking distance and quality of life score in the laboratory can predict longer term effects at home.</p>
Operational Definition	All patients had a stable forced expiratory volume in 1 sec (FEV1) over the preceding 3 months and this was less than 50% predicted normal.
Population	Patients with severe but stable COPD
Intervention	Salbutamol 2.5 mg + ipratropium 0.5mg nebulised and placebo via MDI (active bronchodilators nebulised)
Comparison	Saline nebulized and salbutamol 400µg + ipratropium 80µg via MDI (placebo nebulizer + active BDs by MDI) Salbutamol 400µg + ipratropium 80µg via MDI and no nebulizer issued (always in final period and not blinded)
Outcome	<p>Primary outcomes FEV1, SGRQ scores, 6MWD and home PEF Secondary endpoints TLC and RV, sGaw and diary card symptom scores. Laboratory outcomes Total lung capacity (TLC) / residual volume (RV) / specific airways conductance (sGaw) /FEV1/FVC/SVC/ Hospital Anxiety-</p>

	<p>Depression score/ St George's Respiratory questionnaire (SGRQ)/ 6MWD tests.</p> <p>Patient self-assessment</p> <p>Peak expiratory flow (PEF) / extra inhaled BD usage / nocturnal waken due to dyspnoea/ dyspnoea / effect of dyspnoea on quality of life</p>
Characteristics	<p>11 male and nine female patients</p> <p>Age range 57-79 years</p> <p>All patients had chronic productive cough and were either current smokers of at least 20 pack-years (n = 8) or were ex-smokers.</p> <p>Non had cor pulmonale and none had any other disease which limited either their exercise capacity or dose of bronchodilator.</p> <p>No patients had chest infections within 1 month of starting study.</p> <p>Mean baseline FEV1% predicted of group was 34 ± 8 %</p> <p>Mean baseline 6 Minute Walking Test (6MWD) was 429 m ± 143m</p>
Results	<p>Lung function</p> <p>Treatment with both nebulized and MDI bronchodilators produced significant improvements in lung function with increases in FEV1, FVC, SVC and sGaw and decreases in RV and VAS; however, no significant differences between the treatments were observed.</p> <p>Walking distances</p> <p>Treatment with both nebulized and MDI bronchodilators produced significant improvements in walking distances with an increase in 6MWD and decrease in Borg post-exertional dyspnoea scores; however, no significant differences between the treatments were observed.</p> <p>Post-nebulizer a 30m increase in 6MWD was found in 10 patients.</p> <p>After MDI bronchodilator a 30m increase in 6MWD was found in 8 patients.</p> <p>Quality of life</p> <p>No significant differences in the quality of life scores from the St George's questionnaires and the HAD scores after the three study periods.</p> <p>Peak expiratory flow</p> <p>The mean of the morning and evening PEF readings were significantly better on nebulized drugs compared with MDI; however, this difference was clinically small (17-18 l min⁻¹)</p> <p>Acute or domiciliary assessment</p> <p>Acute improvements in exercise tolerance, exercise-induced dyspnoea, FVC and TLC all correlated significantly, although modestly, with home increases in both perceived dyspnoea and in PEF.</p> <p>Conclusion</p> <p>Salbutamol and Ipratropium bromide given regularly in conventional clinical doses by MDI associated with a spacer produce equivalent bronchodilator responses to much larger nebulized doses. In this study, none of the stable COPD patients benefited from a nebulizer compared with conventional method.</p> <p>Acute changes in FVC and 6MWD may be useful predictors of domiciliary response to bronchodilatory medications in patients.</p>
SIGN Quality Rating	+

Hierarchy of Evidence Grading	1b
NCC CC ID	1429

Author / Title / Reference / Yr	O'Driscoll BR, Kay EA, Taylor RJ, Weatherby H, MCP Chetty, A Bernstein. A long-term prospective assessment of home nebulizer treatment. <i>Respiratory Medicine</i> (1992) 86; 317-325
N=	N= 49 Location=UK
Research Design	Non-randomised prospective study.
Aim	To evaluate home nebulizer treatment in COPD patients who are referred for consideration of such treatment.
Operational Definition	COPD as defined by the American Thoracic Society
Population	n = 34 COPD (n=15 asthma)
Intervention	Home nebuliser (system 22 Acorn nebulizer) administering the following solutions four times daily for 1 months each 1) salbutamol respirator solution 5mg 2) ipratropium bromide unit dose vials 0.5mg; 3) salbutamol 5 mg mixed with ipratropium bromide 0.5mg (always given last due to risk of side effects)
Comparison	Standard therapy (β -agonists and ipratropium bromide by MDI or dry powder inhaler)
Outcome	Pulmonary function / 6MWD / Patient preference
Characteristics	21 male, 13 female 11 current smokers, 22 ex-smokers mean age 61 years (35-75) Mean FEV 0.7l Mean PFR 157 l/min
Results	n = 31 COPD patients completed 1 month of each nebulized treatment Pulmonary function Nebuhaler, salbutamol nebulizer, ipratropium nebulizer and mixed nebulizer gave statistically significantly better PFR responses compared with usual treatment (p = 0.00004, p = 0.03, p = 0.002 and p = 0.01 respectively) No significant difference in PFR responses were seen between mixed nebulizer and the Nebuhaler. (No objective results given – presented as graph) No significant difference in PFR responses was seen when mixed nebulizer was compared with salbutamol nebulizer or ipratropium bromide nebulizer. Patient preference

	3/31 patients preferred their usual MDI (β -agonists and ipratropium bromide by MDI or dry powder inhaler) 9/31 patients chose Nebuhaler 4/31 chose IB nebulizer 7/31 chose salbutamol nebulizer 11/31 chose combined nebulized treatment (salbutamol mixed with IB)
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1432

Author / Title / Reference / Yr	Turner, M. O., Patel, A., Ginsburg, S., FitzGerald, M. (1997). Bronchodilator delivery in acute airflow obstruction: A meta-analysis. Arch Intern Med, 157, 1736-1744.
N=	N=3 studies, N=48 participants Sites=1x Emergency department; 2x Hospital Location=2x United States; 1x not specified
Research Design	RCT
Aim	To compare the effect of bronchodilator delivery by use of a metered-dose inhaler (MDI) or wet nebulizer on objective measurements of acute airflow obstruction in adult patients.
Operational Definition	Operational definition for COPD not given.
Population	Adult COPD patients Berry et al. 1989- N=20 Moss et al., 1985- N=15 Greene and Jackson, 1988- N=13
Intervention	Metered-dose inhaler (N details not split into intervention and comparison)
Comparison	Wet nebulizer
Outcome	FEV1 or PEF
Characteristics	<ul style="list-style-type: none"> • Berry et al. 1989- Mean age=68yrs; Men N=20; • Moss et al., 1985- Mean age=56yrs; Men N=4; • Greene and Jackson, 1988- Mean age=details not available; Men N=not available.
Results	<ul style="list-style-type: none"> • N=3 studies (Berry et al. 1989; Moss et al., 1985; Greene and Jackson, 1988). • N=48 participants

	<ul style="list-style-type: none"> The analysis of 48 patients with COPD from 3 studies gave small treatment effect size of 0.23 (CI, -0.35 to 0.81) SD units that was not significant ($p > .10$). The test of heterogeneity was not significant in the subgroup of COPD patients.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	Ia
Included studies	Berry et al. 1989; Moss et al., 1985; Greene and Jackson, 1988.
NCC CC ID	945

**Section 7.9
Oxygen**

Author	Publication Date	ID	SIGN Grade	Hierarchy
Ram	2003	1796	+	1a
Eaton	2002	19414	+	1b

Author / Title / Reference / Yr	Ram FSF, Wedzicha JA. Ambulatory oxygen for chronic obstructive pulmonary disease. (Cochrane Review). <i>The Cochrane Library. Oxford: Update Software 2003; Issue 3.</i>
N=	N=2 RCTs.; Lilker 1975 N=9 participants; McDonald 1995 N=26 participants Location=(E.g. Australia/Canada) Sites=2 sites. Duration=Long-term follow up (Lilker 1975- 5 weeks; McDonald 1995- 6 weeks)
Research Design	Systematic review of RCT's (double-blind, placebo controlled, cross-over studies)
Aim	To determine the effectiveness of long-term ambulatory domiciliary oxygen therapy in patients with COPD.
Operational Definition	Lilker 1975- recruited patients in their stable condition with a resting arterial oxygen tension (PaO ₂) when breathing room air of less than 60mmHg and who also had cor pulmonale. McDonald 1995- recruited patients who were stable for 3 months or more but who did not have resting hypoxemia (PaO ₂ >60mmHg) or symptomatic cardiac dysfunction, angina pectoris or locomotor disability.
Population	Adult patients with stable chronic COPD. Most of the patients had chronic hypoxaemia (PaO ₂ <7.3 kPa, 55mm Hg) but studies of patients who had PaO ₂ >7.3 kPa at rest and developed exercise hypoxaemia were also included.
Intervention	Long-term ambulatory oxygen therapy through portable oxygen cylinders or with liquid oxygen canisters. Patients must have used oxygen while at home. Lilker 1975 N=9 McDonald 1995 N=26
Comparison	Placebo air cylinders. Lilker 1975 N=9 McDonald 1995 N=26
Outcome	Primary outcome measures - Exercise capacity

	Secondary outcome measure <ul style="list-style-type: none"> - Dyspnoea scores - Arterial oxygen saturation during exercise - Recovery time after exercise - Health status - Lung function measurements
Characteristics	In Lilker 1975- FEV1/FVC 41 %, PCO2 50 mmHg, PO2 53 mmHg, arterial pH 7.38. Mean age not specified. In McDonald 1995- mean age 73yrs, FEV1 0.9 L, resting Po2 69mmHg, resting PCO2 41mmHg and resting SaO2 94%.
Results	90 abstracts were identified for possible inclusion in the review. A total of 17 full text papers were retrieved for possible inclusion. Only 2 studies (McDonald, 1995; Lilker, 1975) were appropriate for inclusion. It was not possible to combine the 2 studies in a meta-analysis. Statistically significant effects of oxygen were only found in Lilker (1975). A decrease in VE with oxygen therapy (WMD-11:00 L/min; 95% CI – 17.53,- 4.47) and a rise in PaO2 at rest (WMD: 17:00 mmHg; 95% CI 9.13, 24.87) compared to placebo was seen. Changes in all other outcomes were not significant, including the distance walked measured using a pedometer, 6 minute walking distance, breathlessness and health related quality of life.
SIGN Quality Rating	+ (The plus SIGN grading is for the methodological quality of the Cochrane review not the included study research results)
Hierarchy of Evidence Grading	Ia
Papers included	Lilker 1975, N=9; McDonald 1995, N=26
NCC CC ID	1796

Author / Title / Reference / Yr	Eaton, T., Garrett, J. E., Young, P., Fergusson, W., Kolbe, J., Rudkin, S., Whyte, K. (2002). Ambulatory oxygen improves quality of life of COPD patients: A randomized controlled study, Eur Respir J, 306-312.
N=	N=41 participants Location: Auckland, New Zealand One site
Research Design	12-week, double-blind randomised crossover study
Aim	The study aims were: 1. To assess the short-term clinical impact, as determined by HRQL, of ambulatory O ₂ in patients with severe COPD and significant exercise desaturation, who did not fulfil criteria for LTOT, and 2. To determine whether either baseline characteristics or acute response predicts short-term response.
Operational Definition	COPD as defined by ATS criteria
Population	Inclusion criteria: COPD, exertional dyspnoea impacting on daily activities, not fulfilling criteria for LTOT, exertional desaturation, ex-smoker and clinically stable for over 2 months with standard optimal medical care.

	Exclusion criteria: important comorbidities.
Intervention	O ₂
Comparison	cylinder compressed air
Outcome	HRQL Chronic respiratory questionnaire Hospital anxiety and depression scale Short form-36 health survey Questionnaire
Characteristics	Age= 67.1 yrs Male %= 70 BMI= 23.7 FEV1 % pred= 25.9 Resting PaO ₂ Kpa=9.2 Resting PaCO ₂ Kpa= 5.8
Results	<p>Short-term responses in health-related quality of life Group analysis of mean differences between cylinder O₂ and cylinder air demonstrated significant improvements in all domains of the disease specific CRQ (Dyspnoea p=0.02; Fatigue p= 0.02; Emotional function p=0.006; Mastery p=0.008) both domains of the HAD (anxiety p=0.009; depression p=0.05) and several domains of the generic SF-36 (role physical p=0.01; general health p=0.04; social functioning p=0.05; role emotional p=0.02) for cylinder O₂ compared with cylinder air.</p> <p>Cylinder gas use A treatment order effect was apparent in that patients who were randomised to cylinder O₂ first had higher weekly use compared to cylinder air (p=0.004). There was no change in the pattern of use over the weeks (p=0.3).</p> <p>Responders to cylinder oxygen Using validated definitions of a minimally clinically important difference, the authors found 28 (68%) acute responders to cylinder O₂ and 23 (56%) short-term responders; 17 (41%) demonstrating both acute and short-term responses. Only seven (17%) patients were defined as neither acute nor short-term responders.</p> <p>Predictors of short-term response to cylinder oxygen No predictors of short-term response were identified.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ib
NCC CC ID	19414

Section 7.10 Non-invasive ventilation

N= 276 Literature search
N= 240 excluded from abstracts
N= 31 full papers ordered and of these;
N= 5 papers critically appraised
N= 26 papers excluded
N= 4 papers found on cross referencing

Author	Publication Date	ID	SIGN Grade	Hierarchy
Wijkstra, P. J., Lacasse, Y., Guyatt, G. H., & Goldstein, R. S. 2002, "Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. [Review] [30 refs]", <i>Cochrane Database of Systematic Reviews</i> . Ref ID: 1482	2002	1482	++	1a
Garrod, R., Mikelsons, C., Paul, E. A., & Wedzicha, J. A. 2000, "Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease", <i>American Journal of Respiratory & Critical Care Medicine</i> , vol. 162, no. 4 I, pp. 1335-1341. Ref ID: 1479	2000	1479	+	1b
Shapiro, S. H., Ernst, P., Gray-Donald, K., Martin, J. G., Wood-Dauphinee, S., Beaupre, A., Spitzer, W. O., & Macklem, P. T. 1992, "Effect of negative pressure ventilation in severe chronic obstructive pulmonary disease", <i>Lancet</i> , vol. 340, no. 8833, pp. 1425-1429. Ref ID: 1474	1992	1474	+	1b
Clini, E., Sturani, C., Rossi, A., et al.	2002	1301	+	1b

2002, "The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients", <i>European Respiratory Journal</i> , vol. 20, no. 3, pp. 529-538. Ref ID: 1301				
Christensen, E. F., Nedergaard, T., & Dahl, R. 1990, "Long-term treatment of chronic bronchitis with positive expiratory pressure mask and chest physiotherapy", <i>Chest</i> , vol. 97, pp. 645-650. Ref ID: 1459	1990	1459	-	1b

Author / Title / Reference / Yr	Wijkstra PJ, Lacasse Y, Guyatt GH, Goldstein RS. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. (Cochrane Review). <i>The Cochrane Library. Oxford: Update Software 2003; Issue 3</i> . Ref ID: 1482
N=	N=4 RCTS
Research Design	Cochrane Review
Aim	To determine the effect of nocturnal non-invasive positive pressure ventilation via nasal mask or face mask in patients with COPD
Operational Definition	Patients with COPD according to the guidelines of American Thoracic Society
Population	Stable patients with COPD
Intervention	Nocturnal non-invasive positive pressure ventilation plus standard therapy
Comparison	Standard therapy alone
Outcome	Blood gases, 6 minute walk (6MWD), dyspnoea (during daily activities), health status (health related quality of life measurements), and respiratory muscle function (muscle strength or muscle endurance, including PI max (maximal inspiratory pressure). Lung function (FEV1 and VC) and sleep efficiency (time asleep as a percentage of total time in bed)
Characteristics	<p>Included studies</p> <p>Strumpf 1991 – Nocturnal positive pressure ventilation via nasal mask in patients with COPD. RCT with crossover comparing nocturnal non invasive Bi-level Positive Airways Pressure (BiPAP) with standard care for a sequential period of 3 months. N = 23</p> <p>Gay 1996 – Nocturnal nasal ventilation in stable, severe COPD. RCT comparing nocturnal BiPAP versus sham treatment. N = 35</p>

	<p>Meecham Jones 1995 – Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. N = 14</p> <p>Casanova 2000 – Nocturnal ventilation by BiPAP plus standard treatment compared with standard treatment. N = 52</p> <p>Studies were excluded if not published in full, not randomised, duration of BiPAP too short, training of BiPAP too short.</p>
Results	<p>The only outcome for which the 95% confidence interval excluded zero was PI max. n = 24 BiPAP n = 24 control; mean effect [95%CI] = 6.2cm H2O [0.2;12.2]</p> <p>The 95% confidence interval of the other outcomes included zero. These included FEV1, FVC, PaCO2, sleep efficiency and 6-minute walking distance (6MWD).</p> <p>FEV1 (n = 33 BiPAP n = 33 control) - mean effect (95% CI) = 0.02L (-0.04; 0.09)</p> <p>FVC (n = 33 BiPAP n = 33 control) - mean effect (95% CI) = -0.01L (-0.14; 0.13)</p> <p>Pimax (n = 24 BiPAP n = 24 control) - mean effect (95% CI) = 6.2 cm H2O (0.2; 12.2)*</p> <p>PEmax (n = 24 BiPAP n = 24 control) - mean effect (95% CI) = 18.4 cm H2O (-11.8; 48.6)</p> <p>PaO2 (n = 33 BiPAP n = 33 control) - mean effect (95% CI) = 0.0 mmHg (-3.8; 3.9)</p> <p>PaCO2 (n = 33 BiPAP n = 33 control) - mean effect (95% CI) = -1.5 mmHg (-4.5; 1.5)</p> <p>6-MWD (n = 12 BiPAP n = 11 control) - mean effect (95% CI) = 27.5m (-26.8; 81.8)</p> <p>The mean effect on 6MWD was modest at 27.5m, but the 95% CI were wide (-26.8, 81.8m) suggesting that some patients had a big improvement.</p> <p>Reviewers' conclusions Nocturnal NIPPV for at least 3 months in hypercapnic patients with stable COPD had no consistent clinically or statistically significant effect on lung function, gas exchange, respiratory muscle strength, sleep efficiency or exercise tolerance; however, the small sample sizes of these studies precludes a definite conclusion regarding the effects of NIPPV in COPD.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
NCC CC ID	Cochrane 1482
Studies Included	Strumpf 1991, Gay 1996, Meecham Jones 1995, Casanova 2000

Author / Title / Reference / Yr	Garrod, R., Mikelsons, C., Paul, E. A., & Wedzicha, J. A. 2000, "Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease", <i>American Journal of Respiratory & Critical Care Medicine</i> , vol. 162, no. 4 I, pp. 1335-1341. Ref ID: 1479
N=	N= 45. Location=UK. Site=outpatient clinic

Research Design	Prospective randomised controlled study
Aim	To determine whether nocturnal domiciliary NPPV provided in conjunction with a pulmonary rehabilitation program can lead to greater improvement in exercise capacity, health status, and respiratory muscle performance than training alone in patients with severe COPD.
Operational Definition	History of severe COPD with forced expiratory volume in 1 sec (FEV1) less than 50% predicted and less than 15% reversibility of FEV1 to inhaled salbutamol (400 µg)
Population	Stable severe COPD
Intervention	Exercise training with noninvasive positive pressure ventilation (ET + NPPV) N=23
Comparison	Exercise training alone N = 22
Outcome	Blood gases/walking distance/time asleep/chronic diseases respiratory questionnaire (CDRQ)
Characteristics	mean (SD) FEV1 0.92 (0.28) L FEV1% predicted 25.2 (12.8) PaO2 65.4 (9.07) mmHg PaCO2 45.6 (7.89) mmHg Age NPPV + ET 63 (38-84 yrs) ET 67 (55 – 70 years) No significant differences between baseline characteristics of groups.
Results	<p>Physiological parameters No significant changes in spirometry parameters to end of study (12 weeks) in both groups</p> <p>FEV1, L NPPV + ET Difference [95% CI) = -0.03 [-0.93 to 0.15] ET Difference [95% CI) = -0.04 [-0.57 to 0.13]</p> <p>FVC, L NPPV + ET Difference [95% CI) = 0.24 [-0.45 to 0.05] ET Difference [95% CI) = -0.05 [-0.63 to 0.25]</p> <p>Arterial blood gases A small but statistically significant increase in PaO2 after the 12 wk time period in the NPPV + ET group (p=0.03) No significant differences in PaCO2 at any time period</p> <p>PaO2,mm Hg NPPV + ET Difference [95% CI) = 2.55 [4.25 to 0.15] p <0.05 ET Difference [95% CI) = -1.58 [-1.16 to 4.20]</p> <p>PaCO2,mm Hg NPPV + ET Difference [95% CI) = -1.3 [-1.35 to 3.98] ET Difference [95% CI) = -1.10 [-0.90 to 3.17]</p> <p>Inspiratory muscle strength</p>

	<p>The NPPV + ET group showed significant increase in inspiratory muscle strength There were no significant changes in expiratory muscle strength (PEmax) in either group</p> <p>Pimax cm H2O NPPV + ET Difference [95% CI) = 6.4 [1.14 to 13.1] p <0.05 ET Difference [95% CI) = 1.10 [-3.71 to 8.81]</p> <p>PEmax cm H2O NPPV + ET Difference [95% CI) = 18.1 [-4.5 to 33.1] ET Difference [95% CI) = -6.5 [-8.56 to 16.4]</p> <p>Walking distance There was a significant increase in walking distance over the trial period in the NPPV + ET group</p> <p>SWT, m NPPV + ET Difference [95% CI) = 100 [58.5 to 141] p <0.001 ET Difference [95% CI) = 28 [-16 to 72]</p> <p>Health Status Measure There was a significant increase in CRDQ total scores in both groups There was a significant difference in the changes in the fatigue component of CDRQ between groups with the NPPV + ET group showing a larger improvement compared with ET group.</p> <p>CRDQ NPPV + ET Difference [95% CI) = 24.1 [15.1 to 33] p <0.001 ET Difference [95% CI) = 11.8 [4.34 to 19.2] p<0.05</p> <p>CRDQ (fatigue) NPPV + ET Difference [95% CI) = 5.9 [3.94 to 7.71] p <0.001 ET Difference [95% CI) = 2.5 [0.44 to 4.36] p<0.05</p> <p>Both groups showed significant differences in activities of daily living scores.</p> <p>LCADL (total) NPPV + ET Difference [95% CI) = -6.7 [-11.5 to -1.94] p <0.001 ET Difference [95% CI) = -6.4 [-10.5 to -2.22] p<0.001</p> <p>No significant differences were observed in the HAD scores in either treatment group.</p> <p>Exercise tolerance During the second month of training, the NIPPV + ET group continued to improve with respect to walking distance from mean (SD) 238 (95.3)m to 290 (118)m (p = 0.003) while the ET group showed no change. There was a mean end study difference (95% CI) between the groups of 65.8m (17.1 to 114), p = 0.009</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b

NCC CC ID	1479
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Author / Title / Reference / Yr	Shapiro, S. H., Ernst, P., Gray-Donald, K., Martin, J. G., Wood-Dauphinee, S., Beaupre, A., Spitzer, W. O., & Macklem, P. T. 1992, "Effect of negative pressure ventilation in severe chronic obstructive pulmonary disease", <i>Lancet</i> , vol. 340, no. 8833, pp. 1425-1429. Ref ID: 1474
N=	N= 184. Location=Canada
Research Design	Randomised controlled, double-blind trial
Aim	To determine whether negative pressure ventilation (NPV) improves ability to exercise, reduces the sensation of dyspnoea and improves the quality of life in patients with severe COPD
Operational Definition	Forced expiratory volume in 1 sec (FEV1) not greater than 50% predicted.
Population	Severe COPD
Intervention	Active negative pressure ventilation (n = 92)
Comparison	Sham negative pressure ventilation (n = 92)
Outcome	Distance walked in 6 minutes/ Cycle endurance time/ dyspnoea / quality of life / maximum inspiratory measure (Pimax)/ maximum expiratory measure (PEmax) / arterial blood gas tensions/ FEV1/forced vital capacity/ single breath diffusing capacity for carbon monoxide/ respirator use
Characteristics	Most patients were men aged 55-70 years with FEV1 f about 30% of predicted. More than 80% of patients had grade 5 dyspnoea according to ATS questionnaire. 70% had baseline PaCO2 below 45mm Hg 13% were receiving supplementary oxygen and 30% had baseline PaCO2 above 45mm Hg. All but 3 patients had at one time smoked. No significant differences in baseline characteristics.
Results	No significant differences in any outcome measure between active and sham groups No significant differences observed during subgroup analysis with results adjusted for baseline value, FEV1, PaCO2, use of oxygen at home and in those patients whose follow-up results were complete. Respirator use High correlation between patient-recorded and clock-metered use of NPV (p=0.91); mean respirator use was 205 (SD 161) hours in the active group and 255 (177) hours in the sham group No dose-response relationship was observed i.e. Number of hours spent using NPV did not correlate with outcomes Exercise 6 minute walk (m)

sham - mean (SD) change; % change = 15.2 (54.5); 7%
active - mean (SD) change; % change = 11.1 (48.9); 5%
Point estimate (95% CI) for active-sham difference = -4.5 (-19.6, 10.8)

Cycle ergometer (minutes)

sham - mean (SD) change; % change = 2 (7.4); 0.6%
active - mean (SD) change; % change = 2.1 (6.9); 0.4%
Point estimate (95% CI) for active-sham difference = -0.15 (-2.27, 1.97)

Dyspnoea grade

sham - mean (SD) change; % change = 6, 78, 16
active - mean (SD) change; % change = 0, 83, 17
Point estimate (95% CI) for active-sham difference = 0.8 (0.39, 1.69)

Dyspnoea transition

sham - mean (SD) change; % change = 10.7 (3.7)
active - mean (SD) change; % change = 10.8 (3.6)
Point estimate (95% CI) for active-sham difference = 0.12 (-0.92, 1.17)

Oxygen cost score

sham - mean (SD) change; % change = 8.2 (19.4); 29%
active - mean (SD) change; % change = 4.2 (22.9); 14%
Point estimate (95% CI) for active-sham difference = -2.04 (-7.39, 3.31)

Quality of life

sham - mean (SD) change; % change = 0.5 (1.9); 13%
active - mean (SD) change; % change = 0.8 (1.9); 15%
Point estimate (95% CI) for active-sham difference = 0.34 (-0.28, 0.75)

Gas exchange

PaO2 (mm Hg)

sham - mean (SD) change; % change = -0.9 (9.8); -0.4%
active - mean (SD) change; % change = -0.8 (7.0); -0.8%
Point estimate (95% CI) for active-sham difference = -0.24 (-2.45, 1.97)

PaCO2 (mm Hg)

sham - mean (SD) change; % change = -0.1 (2.9); -0.2%
active - mean (SD) change; % change = -0.2 (2.6); -0.4%
Point estimate (95% CI) for active-sham difference = -0.11 (-0.9, 0.68)

Pimax (cm H2O)

sham - mean (SD) change; % change = 1.4 (12.8); 6%
active - mean (SD) change; % change = 3.2 (13.1); 9%

	Point estimate (95% CI) for active-sham difference = 1.31 (-2.46, 5.08) PEmax (cm H2O) sham - mean (SD) change; % change = 3.3 (23.0); 9% active - mean (SD) change; % change = -1.7 (27.5); 10% Point estimate (95% CI) for active-sham difference = -4.94 (-11.68, 1.80)
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1474

Author / Title / Reference / Yr	Clini, E., Sturani, C., Rossi, A., Viaggi, S., Corrado, A., Donner, C. F., Ambrosino, N., Murgia, A., DeMurtas, R., Polverino, M., Grisolia, M. A., Marcolongo, A., Confalonieri, M., Gorini, M., Villella, G., Garuti, G., Clini, E., Vitacca, M., Scarduelli, C., Amaducci, S., Iuliano, A., Sergi, M., Rizzi, M., Nava, S., Squillante, F., Cassandro, R., Bevilacqua, M., Marchese, S., LoCoco, A., Cerveri, I., Pasi, A., Dottorini, M., Baglioni, S., Ferranti, P., Tazza, R., Palla, A., Desideri, M., Muir, J. F., Damato, S., Marino, P., Peratoner, A., & Zaccaria, S. 2002, "The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients", <i>European Respiratory Journal</i> , vol. 20, no. 3, pp. 529-538. Ref ID: 1301
N=	N= 90 Location=Italy
Research Design	Prospective randomised controlled trial
Aim	To assess the effect of Non-invasive positive pressure ventilation (NPPV) + Long Term Oxygen Therapy (LTOT) on: 1) severity of hypercapnia; 2) use of healthcare resources, and 3) health related quality of life in comparison with LTOT alone
Operational Definition	Diagnosis of chronic ventilatory failure based on values of PaCO ₂ > 6.6 kPa (50mmHg) during room air spontaneous breathing. All patients were in stable clinical condition, as assessed by arterial pH >7.35 and were free from exacerbation in the 4 weeks preceding treatment.
Population	Stable hypercapnic COPD patients on long term oxygen therapy for ≥6 months
Intervention	NPPV + LTOT (n=43)
Comparison	LTOT alone (N = 47)
Outcome	Arterial blood gases / hospital and intensive care unit (ICU) admissions / total hospital and ICU length of stay / HRQL / survival and drop-out rates / symptoms (dyspnoea and sleep quality) / exercise tolerance
Characteristics	age ≤ 75 years Males 69: females 17

	<p>LTOT for at least 6 months dyspnoea score as assessed by MRC score ≥ 2 FEV1 <1.5L FEV1 to FVC ratio < 60% total lung capacity $\geq 90\%$ predicted PaCO₂ > 6.6kPa (50mmHg) Arterial oxygen tension < 7.8kPa (60 mmHg) At baseline all characteristics were similar</p>
<p>Results</p>	<p>Treatment compliance NPPV + LTOT - mean daily LTOT use = 19 ± 1 h LTOT alone - mean daily LTOT use = 20 ± 2 h</p> <p>Physiological variables No significant differences in lung function, inspiratory muscle function, exercise tolerance and sleep quality score</p> <p>Arterial Blood Gases No significant differences between groups was found in ABG during room air breathing.</p> <p>PaCO₂ Over two years of treatment PaCO₂ on usual oxygen averaged 7.23 and 7.89 kPa (55 and 60 mmHg) in NPPV + LTOT and LTOT respectively. PaCO₂ exhibited a tendency to increase in LTOT patients, whereas it consistently decreased in NPPV + LTOT patients Month 12 treatment effect 2.997, 95% confidence interval 0.94-5.05 (p = 0.005) Month 24 treatment effect 4.270, 95% confidence interval 1.58-9.96 (p = 0.002)</p> <p>Dyspnoea Resting dyspnoea significantly improved over time in the NPPV + LTOT group and at month 24 was significantly better than in the LTOT alone group. Month 12 treatment effect 0.4, 95% confidence interval 0.02 – 0.78 (p = 0.048) Month 24 treatment effect 0.6, 95% confidence interval 0.15 - 1.05 (p = 0.013)</p> <p>Health Related Quality of Life After 2 years SGRQ total score showed a trend to improve in both groups (-5 and -4% in NPPV + LTOT and LTOT alone groups respectively) (p=0.554) The MRF-28 total score significantly improved in the NPPV + LTOT group compared to the LTOT group Treatment effect 7.1, 95% confidence interval 0.13-4.07 (p=0.041)</p> <p>Hospitalisations Hospital admissions were not significantly different between groups during follow-up. NPPV + LTOT - mean hospital admissions per patient per year = 0.9 ± 1.2 LTOT alone - mean hospital admissions per patient per year = 1.4 ± 2.3 ICU admissions were not significantly different between groups during follow-up.</p>

	<p>NPPV + LTOT - mean hospital admissions per patient per year = 0.2 ± 0.4 LTOT alone - mean hospital admissions per patient per year = 0.4 ± 0.8 Compared with the 3 year period before the start of the study, ICU stay decreased over time by 75% and 20% in the NPPV and LTOT and LTOT groups, respectively; however differences between groups were not significant</p> <p>Conclusion The addition of non-invasive positive pressure ventilation to long-term oxygen therapy in stable COPD patients with chronic ventilatory failure is able to</p> <ol style="list-style-type: none"> 1) improve daytime carbon dioxide in arterial blood during oxygen breathing; 2) improve dyspnoea and health-related quality of life.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1301

Author / Title / Reference / Yr	Christensen, E. F., Nedergaard, T., & Dahl, R. 1990, "Long-term treatment of chronic bronchitis with positive expiratory pressure mask and chest physiotherapy", <i>Chest</i> , vol. 97, pp. 645-650. Ref ID: 1459
N=	N= 54. Location=Denmark
Research Design	Prospective randomised controlled trial
Aim	To compare the prophylactic effect of diaphragmatic breathing and forced expirations with and without PEP-mask in the home treatment of patients with chronic bronchitis.
Operational Definition	Cough daily and expectoration for at least three consecutive months for the last two years
Population	Chronic bronchitis
Intervention	PEP treatment where diaphragmatic breathing was performed through a positive expiratory pressure (PEP) mask followed by forced expirations and cough
Comparison	Self administered diaphragmatic breathing followed by forced expiration and cough until expectoration succeeded (n = 20)
Outcome	Symptoms/ number of acute exacerbations / number of sick-leaves / need for additional medication (including antibiotics)/ lung function tests
Characteristics	<p>Age – PEP 61.7 (4.6) Control 62.7 (5.2) FEV1,L - PEP 1.72 (0.73) Control 2.07 (0.57) Duration of disease - PEP 18.4 (15.7) Control 12.6 (10.7) Baseline characteristics further detailed in table</p>

	At baseline all characteristics were similar. No significant differences between the control group and the PEP group with respect to age, smoking habits, duration of disease, number of acute exacerbations during previous year, other treatments and medication.
Results	<p>Compliance From diary card entries daily use of treatments was calculated PEP mask – mean daily use 2.5 times (1.8 to 4.6) Control – mean daily use of physiotherapy 2.5 times (range 0.7 to 6.1)</p> <p>Symptoms From diary cards; PEP group reported significantly less cough (p=0.025), significantly less mucus production (p= 0.013) compared with the control group The overall assessment of the treatment after one month and at the end of the study was significantly more positive in the PEP group (p<0.05)</p> <p>Acute exacerbations The PEP group had fewer acute exacerbations compared with the control group (6 vs 28) The number of patients who experienced acute exacerbations were smaller in the PEP group compared with the control group (3 vs 12) In the PEP group, 85% of patients remained free from acute exacerbations compared with 48% in the control group (p=0.011) The exacerbation rate was significantly lower in the PEP group compared with the control group (p<0.0005)</p> <p>Sick leaves (only a few patients were still working) In the PEP group 17 days were spent on the sick list compared with 64 in the control group</p> <p>Antibiotics The number of diary days with use of antibiotic was less in the PEP group compared with the control group (21 vs 74 days)</p> <p>Mucolytics The use of acetylcysteine and other mucolytic drugs was significantly lower in the PEP group compared with the control group (p<0.05)</p> <p>Lung function No significant difference in lung function between the groups.</p>
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1459

Section 7.12 Pulmonary rehabilitation

N=609 Literature search
N=42/609 selected by Clinical Lead from abstracts.
N=29/42 excluded by Systematic Reviewer on full paper review
N=12 critically appraised and evidence tables compiled
N=2 sets of guidelines for which evidence tables compiled
N=7 papers suggested by members of the GDG critically appraised and evidence tables compiled*.
N=21 Evidence pulmonary rehabilitation tables available
References suggested by members of the GDG*

Evidence Table ID	Author
Cited in evidence statements (in order of statement)	
ID 63	ACCP Guidelines (Ries) 1997
ID 1157	Lacasse Cochrane 2002
ID 1223	BTS Guidelines 2001
ID 1024/1020	Toshima 1992
ID 1041 (No evidence table as already included in the Lacasse Cochrane Systematic Review (ID 1157))	Griffiths 2000
ID 49	Ries 1995
ID 894	Smith 1992
ID 1227	Lotters 2002*
ID 1228	Puente-Maestu 2000*
ID 1040	Young 1999
ID 1045	Foglio 2001
ID 1226	Roomi 1996*
ID 74	van 't Hul 2002
Other evidence tables submitted to the GDG but excluded from evidence statements	
ID 1030	Wijkstra 1995
ID 1033	Wijkstra 1996
ID 1043	Troosters 2000
ID 1047	Green 2001

ID 222	Wedzicha 1998*
ID 235	Lacasse 1996
ID 1051	Brooks 2002
ID19370	Berry, M. J 2003
ID 19351	Salman et al 2003
ID 19373	Ortega et al 2003
ID 19371	Bestall et al 2003
Additional references suggested by members of the GDG but excluded from evidence statements	
ID 1230	Chavannes 2002*
ID 236	Strijbos 1996*
ID 1224	Troosters 2001*

Author / Title / Reference / Yr	Ries, A. L., Carlin, B. W., Carrieri-Kohlman, V., Casaburi, R., CELLI, B. R., Emery, C. F., Hodgkin, J. E., Mahler, D., Make, B., & Skolnick, J. 1997, "Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines ", <i>Chest</i> , vol. 112, no. 5, pp. 1363-1396. Ref ID: 63
N=	Lower Extremity Training – N=12 RCTs / Non randomised controlled trials N=2 Upper Extremity Training – N=5 RCTs Ventilatory Muscle Training – N=1 Meta-analysis of 17 trials / N=6 RCTs VMT and Exercise Training – N=5RCTs Psychosocial / Behavioural / Educational Interventions – N=4RCTs / N=1 Observational study Pulmonary Rehabilitation on Psychosocial / Behavioural Factors – N=3RCTs / N=4 Observational studies Dyspnoea – N=5RCTs / N=1 Non randomised controlled trial Health Related Quality of Life Tools for Assessment – N=5 studies Effect of Pulmonary Rehabilitation on QoL – N=3RCTs Effect of Limited pulmonary Rehabilitation on QoL – N=3RCTs / N=3 Non randomised trials Effect of Pulmonary Rehabilitation on Employment – N=2 Effects of pulmonary Rehabilitation on Health-Care Utilisation – N=2RCTs / N=2 Non-randomised controlled trials / N=8 Observational studies. Effects of Pulmonary Rehabilitation on Survival – N=1 RCT / N=1 Non-randomised controlled trial / N=4 Observational studies.
Research Design	Evidence Based Guidelines
Aim	The primary purpose of the document is to review the scientific basis for pulmonary rehabilitation.
Operational Definition	COPD not defined.
Population	Adults with COPD
Intervention	As above (cited in “N=” section)
Recommendations	<p>Lower Extremity Training “Patients with COPD who undergo a program of lower extremity exercise training consistently improve measures of exercise tolerance without evidence of adverse outcome. A program of exercise training of the muscles of ambulation is recommended as apart of pulmonary rehabilitation for patients with COPD (Strength of Evidence =A)”.</p> <p>Upper Extremity Training “Strength and endurance training of the upper extremities improves arm function in patients with COPD. Arm exercises are safe, and should be included in rehabilitation programs for patients with COPD. (Strength of Evidence =B)”.</p> <p>Ventilatory Muscle Training The scientific evidence at the present time does not support the routine use of VMT as an essential component of pulmonary rehabilitation. However, VMT may be considered in selected patients with COPD who have decreased respiratory muscle strength and breathlessness. (Strength of Evidence = B)”.</p>

	<p>Psychosocial, Behavioural and Educational Components and Outcomes “Evidence to date does not support the benefits of short-term psychosocial interventions as single therapeutic modalities, but longer-term interventions may be beneficial. Although scientific evidence is lacking, expert opinion supports the inclusion of educational and psychosocial intervention as components of comprehensive pulmonary rehabilitation programs for patients with COPD. (Strength of Evidence = C)”.</p> <p>Dyspnoea “Pulmonary rehabilitation improves the symptoms of dyspnoea in patients with COPD. (Strength of Evidence = A)”.</p> <p>Quality of Life “Pulmonary rehabilitation improves health-related QoL in patients with COPD. (Strength of Evidence = B)”.</p> <p>Health Care Utilisation “Pulmonary rehabilitation has reduced the number of hospitalisations and the number of days of hospitalisations for patients with COPD. (Strength of Evidence = B)”. N.B American Guidelines.</p> <p>Survival “Pulmonary rehabilitation may improve survival in patients with COPD. (Strength of Evidence = C)”.</p>
AGREE Appraisal of Guidelines for Research & Evaluation Instrument.	Fits criteria for “Strongly recommend”
Hierarchy of Evidence Grading	1a
NCC CC ID	63

Author / Title / Reference / Yr	Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH <i>et al.</i> Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease.(Cochrane Review). <i>The Cochrane Library.Oxford:Update Software 2003;Issue 3.</i> Ref ID: 1157
N=	N=23 trials
Research Design	Cochrane systematic review. Updates reported by Lacasse et al Lancet 1996 748:1115-1119
Operational Definition	More than 90% of pts had COPD defined as 1) a clinical diagnosis of COPD, 2) one of the following; a) best recorded FEV1/FVC ratio of individual pts <0.7; b) best recorded FEV1 of individual pts <70% of predicted value.
Population	COPD
Intervention	Pulmonary rehabilitation (defined as exercise training for at least 4 wks with or without education and or psychological support.

	In-patient, out patient or home based rehabilitation program of at least 4 wks duration that included exercise therapy with or without any form of education and / or psychological support delivered to pts with exercise limitation attributable to COPD.
Comparison	Conventional community care
Outcomes	QoL / functional or maximal exercise capacity
Characteristics	Baseline characteristics split per trial, not presented as total. Mean age range=55-73 / 59% Male / Ethnic origin not detailed
Results	<p>Statistically significant improvements were found for all the outcomes.</p> <p>HRQOL</p> <p>In three domains of QoL (CRQ for dyspnoea, fatigue and mastery) the effect was larger than the minimal clinically important difference of 0.5 units.</p> <p>For HRQOL the analysis was restricted to the CRQ as it represented the most widely used questionnaire across the trials</p> <p>Results presented below are of the CRQ on a 7-point scale (those results presented in <i>italicised brackets</i> are of the total score of each of the questionnaires domains).</p> <p>Dyspnoea (9 trials, N=519) WMD 1.0 CRQ units 95% CI; 0.8-1.2 p=0.53* (<i>WMD 5.1; 95% CI; 4.04-6.1</i>)</p> <p>Fatigue (8 trials, N=513) WMD 0.9 CRQ units 95% CI; 0.7-1.1 p=0.48* (<i>WMD 3.5; 95% CI; 2.7-4.4</i>)</p> <p>Emotional function (8 trials, N=513) WMD 0.7 CRQ units 95% CI; 0.4-1.0 p=0.17* (<i>WMD 4.9; 95% CI; 3.0-6.8</i>)</p> <p>Mastery (8 trials, N=513) WMD 0.9 CRQ units 95% CI; 0.7-1.2 p=0.87* (<i>WMD 3.7; 95% CI; 2.8-4.6</i>)</p> <p>(*p values are for homogeneity)</p> <p>Functional exercise capacity</p> <p>For FEC and MEC the effect was small and a little below the threshold of clinical significance for the 6 minute walking distance. (10 trials, N=454) WMD 49 meters 95% CI; 26-72</p> <p>*p=0.08 Heterogeneity was found among study results which none of the subgroup analyses explained.</p> <p>Maximum exercise capacity</p> <p>(14 trials, N=488) WMD 5.4 watts 95% CI; 0.5-10.2 *p=0.14</p> <p>NB Homogeneity across studies was tested for each outcome, heterogeneity was declared when p was <0.10</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
NCC CC ID	1157
Studies included	Bendstrup 1997, Booker 1984, Busch 1988, Cambach 1997, Clark 1996, Cockcroft 1981, Emery 1998, Engstrom 1999, Goldstein 1994, Gosselink 2000, Griffiths 2000, Guell 1995, Hernandex 2000, Jones 1985, Lake 1990, McGavin 1977, Reardon 1994, Ringbaek 2000, Simpson 1992, Strijbos 1996, Vallet 1994, Weiner 1992, Wijkstral 1994.

Author / Title / Reference / Yr	British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation 2001, "Pulmonary rehabilitation. [Review] [87 refs]", <i>Thorax</i> , vol. 56, no. 11, pp. 827-834. Ref ID: 1223
Research Design	BTS Statement
Aim	"Summaries of the scientific evidence and recommendations for practice have recently been published by the American Thoracic Society and in the ACCP / AACVPR evidence-based guidelines. This document from the BTS is therefore not intended to become another new set of guidelines but, instead, will develop these existing publications and introduce more recent evidence. The purpose is to summarise the available evidence for both the process and benefits of pulmonary rehabilitation to convince providers, commissioners, and consumers of health care to introduce a worthwhile service".
Operational Definition	Operational definition of COPD is not provided.
Population	COPD
Intervention	<p>"The process of pulmonary rehabilitation Site and personnel / Format, content and benefits / Dose response effect and maintenance / Cost / Safety Issues</p> <p>The components of rehabilitation Physical training / Endurance (aerobic) training / Strength training / Respiratory muscle training / Use of Oxygen during exercise training / Education / Psychology and behavioural intervention / Physiotherapy, relaxation exercises and energy conservation / Nutrition / Rehabilitation and lung volume reduction surgery".</p>
Evidence	<p>"Evidence exists that a multiprofessional individually tailored programme of rehabilitation including prescribed endurance exercise training should:</p> <p>Improve functional exercise capacity [1a] Improve health status [1a] Reduce dyspnoea [1a] Have some health economic advantages [1b]"</p>
Results	<p>"Summary of key points</p> <p>Selection Although most patients will have COPD, the benefits of rehabilitation may apply to all patients with dyspnoea from respiratory disease. [B] The introduction of rehabilitation becomes appropriate when patients become aware of their disability. Rehabilitation should be considered at all stages of disease progression when symptoms are present and not at a predetermined level of impairment. This would usually be MRC dyspnoea grade 3 or above. [C] There is currently no justification for selection on the basis of age, impairment, disability, or smoking status. Some patients with serious co-morbidity such as cardiac or locomotor disability may not benefit as much. [B]</p>

The only issues material to selection are poor motivation and the logistical factors of geography, transport, equipment usage, and the group composition. [C]

Setting

Pulmonary rehabilitation is effective in all settings including hospital inpatient, hospital outpatient, the community, and the home.

[A]

Cost comparison suggests that hospital outpatient rehabilitation is currently the most efficient form of delivery. [C]

Programme content

Outpatient programmes should contain a minimum of 6 weeks of physical exercise, disease education, psychological, and social intervention. [B]

Physical aerobic training, particularly of the lower extremities (brisk walking or cycling), is mandatory. [A]

Upper limb and strength building exercise can be included. [B]

Exercise prescription should be precise and individually assessed. [C]

Individual training intensity should be recorded and can be increased through the programme where tolerated. [C]

Training intensity should usually be 60–70% of VO₂peak (this can be derived from SWT performance). However, benefit can be obtained from lower intensity training where necessary, and increased benefits can be obtained from higher intensity training (85% VO₂peak) when this can be achieved. [C]

Training frequency should involve three sessions (20–30 minutes) per week of which at least two should be supervised. [C]

Supplementary oxygen during training should be provided where clinically important desaturation is documented at the training workload. [C]

Comprehensive disease education for patient and family is an important part of overall management that can be conducted within the rehabilitation programme. [C]

Access to individual advice on physiotherapy, nutrition, occupational therapy, smoking cessation, end of life planning, and physical relationships is desirable. [C]

Process

A nominated clinician with an interest in respiratory disease should be responsible for the programme. This clinician should normally be responsible for medical assessment prior to entry to the programme. [C]

The programme should have a responsible officer appointed for the purpose. The coordinator may come from a profession allied to medicine or nursing. [C]

Staffing ratios will vary according to the patient characteristics, but a staff / patient ratio of 1:8 would be reasonable for the supervision of exercise classes. [C]

There should be multiprofessional involvement from local resources. [C]

Policies should exist for the stages of rehabilitation, which include referral, assessment, selection, rehabilitation, and outcome assessment. [C]

Regular audit of the programme is desirable. [C]

Outcome measures

	<p>These should be embedded in the programme as part of the process. [C]</p> <p>The outcome measures should reflect the goals of rehabilitation by examination of relevant impairment, disability, handicap, and domestic activity. [C]</p> <p>Outcome measures need only be simple but centers with expertise can use advanced technology. [C]”</p>
Quality Rating	Not critically appraised – “Statement document”
Hierarchy of Evidence Grading	<p>Does not fit into currently used “Hierarchy of Evidence”. Evidence and consensus document.</p> <p>“New references are cited where assertions are not supported in the existing statements and guidelines.” “Strength of evidence was agreed by consensus and is described according to the accepted convention”.</p> <p>Levels of evidence and grading of recommendations are provided.</p>
NCC CC ID	1223

Author / Title / Reference / Yr	<p>Toshima, M. T., BLUMBERG, E., RIES, A. L., & KAPLAN, R. M. 1992, "Does rehabilitation reduce depression in patients with chronic obstructive pulmonary disease?", <i>Journal of Cardiopulmonary Rehabilitation</i>, vol. 12, no. 4, pp. 261-269. Ref ID: 1024</p> <p>“Previously reported preliminary results from an experimental trial evaluating a comprehensive rehabilitation program for pts with COPD (Ref Toshima, M. T., KAPLAN, R. M., & RIES, A. L. 1990, "Experimental evaluation of rehabilitation in chronic obstructive pulmonary disease: short-term effects on exercise endurance and health status", <i>Health Psychology</i>, vol. 9, pp. 237-252. Ref ID: 1020</p> <p>The methodology and results for both of these papers have been incorporated into this evidence table.</p>
N=	N=119 Duration=8wks Location=USA
Research Design	RCT
Aim	Evaluated changes in depression in same pts before and after participation in rehabilitation or education programs
Operational Definition	Clinical diagnosis of COPD confirmed by spirometry – levels not given.
Population	Mild to severe COPD (asthma excluded)
Intervention	Rehabilitation program (N=57)
Comparison	Education control group (N=62). The education group received only information without specific instruction or physical activity training.
Outcomes	Pulmonary function tests / Maximum exercise test / Endurance walk test / Depression (Centres for Epidemiological Studies

	Depression Scale (CES-D) / Efficacy / Social support questionnaire (SSQ) / Index of Activities of Daily Living (ADL).
Characteristics	Concomitant medications – Not detailed Age – Mean 63yrs) Sex – 74% males Ethnic origin – Not detailed Mean FEV1 at screening visit was 1.23 litres (SD 0.55) prebronchodilator (45% predicted) and 1.41 litres (SD 0.64) postbronchodilator (52% of predicted).
Results	Exercise endurance improved significantly for the rehabilitation group but not for the control group (p<0.0001). There were no significant differences in depression between rehabilitation and control subjects at any follow-up period. There were greater increases over time in self efficacy (walking ratings) for the rehabilitation group than for the education group as indicated by a significant group by time interaction (p<0.008), although the two groups were not statistically different by means test at 6/12. Although the rehabilitation pts demonstrated functional improvements and increased self efficacy, they did not demonstrate lower levels of depression. There were no significant differences in depression between rehabilitation and control subjects at any follow up period. Correlation analyses of <i>baseline data</i> for all pts combined showed small non significant correlations between depression and physiologic variables. Depression was significantly correlated (p<0.05) with subjective ratings of dyspnoea, performance of activities of daily living, treadmill performance, self efficacy expectations, social support quantity and social support satisfaction.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1024 and 1020

Author / Title / Reference / Yr	Ries, A. L., Kaplan, R. M., Limberg, T. M. K., & Prewitt, L. M. 1995, "Effects of pulmonary rehabilitation on physiological and psychosocial outcomes in patients with chronic obstructive pulmonary-disease", <i>Annals of Internal Medicine</i> , vol. 122, no. 11, pp. 823-832. Ref ID: 49
N=	N=119. Duration=8 wk programme (pts were followed for 6 yrs). Location=Outpatients from University Medical Centre USA
Research Design	RCT
Aim	As per title
Operational Definition	-
Population	Stable mild to severe COPD. Pts with emphysema, chronic bronchitis or asthmatic bronchitis were included.

	Pts with primarily acute, reversible airway disease (asthma) but no chronic airflow obstruction were excluded.
Intervention	Comprehensive pulmonary rehabilitation, 12 four hr sessions. Monthly reinforcement sessions were held for 1 yr.
Comparison	Education alone, 4 two-hr sessions, videos, lectures and discussions but no individual instruction or exercise training.
Outcomes	Pulmonary function, exercise tolerance and endurance, gas exchange, breathlessness, muscle fatigue with exercise, shortness of breath, self-efficacy for walking, depression, quality of well being and hospitalisations
Characteristics	Baseline variables for Rehab (RB) vs Education (ED) groups Age – 62yrs (RB) / 64 yrs (ED) Male / Female – 42/15 (RB) / 54/17 (ED) Ethnic origin – not detailed Mean FEV1 at screening visit was – FEV1/FVC % 54 (13) (RB) / 43 (10) (ED) Concomitant medications – not detailed
Results	There were no statistically significant findings for the education group compared to pulmonary rehabilitation group Compared with education alone, pulmonary rehabilitation produced a significantly greater increase in: Maximal exercise tolerance; +1.5 metabolic equivalents (METS) compared with +0.6 METS; p<0.001 Maximal oxygen uptake; +0.11 L/min compared with +0.03 L/min; p=0.06 Exercise endurance; +10.5 mins compared with +1.3 mins; p<0.001 Symptoms of perceived breathlessness; score of –1.5 compared with +0.2; p<0.001 Muscle fatigue; score of –1.4 compared with –0.2; p<0.01 Shortness of breath; score of –7.0 compared with +0.6; p<0.01 Self efficacy for walking; score of +1.4 compared with +0.1; p<0.05 There were non significant findings for: Survival and duration of hospital stay. Measures of lung function, depression and general quality of life did not differ between groups. After the 2/12 core rehabilitation program and the 1 yr monthly reinforcements, group differences gradually declined. The benefits persisted for as long as 6/12 for perceived muscle fatigue ratings during exercise and breathlessness with daily activities, for as long as 12/12 for maximum treadmill workload and exercise endurance, for as long as 18/12 for walking self efficacy and for as long as 24/12 for ratings of perceived breathlessness during exercise. Conclusion: Pulmonary rehabilitation significantly improved exercise performance and symptoms for pts with moderate to severe chronic COPD. Benefits were partially maintained for at least 1 yr and tended to diminish after that time.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	49

Author / Title / Reference / Yr	Smith, K., Cook, D., Guyatt, G. H., Madhavan, J., & Oxman, A. D. 1992, "Respiratory muscle training in chronic airflow limitation: a meta-analysis", <i>American Review of Respiratory Disease</i> , vol. 145, no. 3, pp. 533-539. Ref ID: 894
N=	N= 17 RCTs
Research Design	Meta analysis
Aim	Determine the effect of respiratory muscle training on muscle strength and endurance, exercise capacity and functional status in pts with chronic airflow limitation.
Operational Definition	Chronic airflow limitation: a clinical diagnosis of chronic airflow limitation and one of the following: 1) best recorded FEV1/FVC ratio of each subject <0.7; 2) best recorded FEV1 of each subject <70% of predicted; 3) mean FEV1 of the group <35% of predicted; 4) mean FEV1/mean FVC ratio of the group<0.5
Population	Chronic airflow limitation
Intervention	Respiratory muscle training, specifically resistive breathing exercises or isocapnic hyperventilation
Comparison	Not specified
Outcomes	Pulmonary function, respiratory muscle strength, respiratory muscle endurance, laboratory exercise capacity, functional exercise capacity or functional status
Characteristics	Demographic characteristics not detailed.
Results	<p>There is little evidence of clinically important benefit of respiratory muscle training in pts with CAL All results taken from Table 3, p537</p> <p>FEV1 (8 trials) Effect size 0.12 (SD units); 95% CI -0.15-0.39; (Effect size in natural units 41 ml); p=0.38 Homogeneity p value=0.18</p> <p>Respiratory muscle strength (maximum inspiratory pressures) (11 trials) Effect size 0.15 (SD units); 95% CI -0.09-0.39; (Effect size in natural units 3.0 cm); p=0.23 Homogeneity p value=0.21 (NB different values given in abstract)</p> <p>Respiratory muscle strength (maximum voluntary ventilation) (7 trials) Effect size 0.43 (SD units); 95% CI 0.07-0.80; (Effect size in natural units 8.8 L); p=0.02 Homogeneity p value=0.28 (NB same values given in abstract)</p> <p>Respiratory muscle endurance (9 trials) Effect size 0.22 (SD units); 95% CI -0.03-0.48; (Effect size in natural units 37.3 L/min) p=0.09 Homogeneity p value=0.33 (NB different values given in abstract)</p> <p>Laboratory exercise capacity (9 trials) Effect size -0.04 (SD units); 95% CI -0.22-0.14; (Effect size in natural units -0.036 ml/kg/min); p=0.22 Homogeneity p value 0.04 (statistically significant) (NB different values given in abstract)</p>

	<p>Functional exercise capacity (9 trials) Effect size 0.20 (SD units); 95% CI -0.06-0.45; (Effect size in natural units 40.7m); p=0.13 Homogeneity p value 0.25 (NB different values given in abstract)</p> <p>Functional status (QoL) (5 trials) Effect size 0.12 (SD units); 95% CI -0.18-0.42; (Effect size in natural units 0.67 on dyspnoea scale of CRQ); p=0.44 Homogeneity p value 0.04 (statistically significant) (NB different values given in abstract)</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
NCC CC ID	894
Studies included	Chen 1985, Falk 1985, Harver 1989, Nosedá 1987, Belman 1988, Guyatt 1991, Levine 1986, Asher 1982, McIntosh 1987, Larson 1988, McKeon 1986, Reis 1986, Goldstein 1989, Kim 1984, Sobush 1986, Bjerre-Jepson 1981, Dekhuijzen 1991.

Author / Title / Reference / Yr	Lotters, F., van Tol, B., Kwakkel, G., & Gosselink, R. 2002, "Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. ", <i>European Respiratory Journal</i> , vol. 20, no. 3, pp. 570-576. Ref ID: 1227
N=	15 studies. Overall treatment group N=200, control group N=183. Location=Netherlands.
Research Design	Meta analysis
Aim	To provide an update on the efficacy of inspiratory muscle training through a meta analysis of studies evaluating the efficacy of IMT in patients with COPD. Special attention is given to patient characteristics that may influence the efficacy of IMT, in order to select the appropriate patients with COPD for the application of IMT.
Operational Definition	Not specified, only states "Pulmonary function tests must have been conducted".
Population	Only patients with COPD
Intervention	Pts in the treatment group received inspiratory muscle training at an intensity of >30% PI, max .
Comparison	Not specified
Outcomes	PI.max / inspiratory muscle endurance / dyspnoea rating / 6- or 12-min waking distance (6- or 12 MWD) / health related quality of

	life.
Characteristics	Age 63yrs (N=200) FEV1 43 +/- 15% (N=171) PI,max 71+/- 21% (N=200) PaCO2 41 +/-6 mmHg (N=148)
Results	<p>Significant summary effect-size (SES) was found for inspiratory muscle strength, endurance and dyspnoea.</p> <p>Muscle strength and endurance Both IMT alone and IMT as adjunct to general exercise reconditioning significantly increased inspiratory muscle strength (Weight averaged effect size 0.56, 95% CI 0.35 to 0.77) and endurance (0.41, 95% CI 0.14 to 0.68).</p> <p>Dyspnoea A significant effect was found for dyspnoea (TDI) at rest (2.3, 95% CI 1.44 to 3.15) and during exercise.</p> <p>Functional exercise capacity Improved functional exercise capacity tended to be an additional effect of IMT alone and as an adjunct to general exercise reconditioning, but this trend did not reach statistical significance.</p> <p>Patient characteristics No significant correlations were found for training effects with patient characteristics</p> <p>Subgroup analysis Subgroup analysis in IMT plus exercise training revealed that patients with inspiratory muscle weakness improved significantly more compared to patients without inspiratory muscle weakness. In the 15 studies, two types of inspiratory muscle loading were applied; targeted resistive training and training with a threshold-loading device. Subgroup analysis revealed that there were no differences in the outcome of inspiratory muscle strength and inspiratory muscle endurance regarding the different types of training.</p> <p>Quality of Life Meta analysis was not performed on health related quality of life since different outcome measures were used.</p> <p>Homogeneity The homogeneity test statistic was not significant for all outcomes.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
Source	Paper suggested by member of GDG
NCC CC ID	1227
Studies Included	From the 15 studies included in the meta analysis. five had also been included in the meta analysis of Smith et al (1992) marked

	<p>with *.</p> <p>*Belman MJ, Shadmehr R (1988), Berry MJ, Adair NE, Sevensky KS et al (1996), *Dekhuijzen PN, Folgering HT, van Herwaarden CL et al 1991), *Goldstein R, De Rosie J, Long S et al (1989), *Harver A, Mahler DA, Daubenspeck JA (1989), Keijdra YF, Dekhuijzen PN, van Herwaarden CL et al (1996), Kim MJ, Larson JL, Covey MK et al (1993), *Larson JL, Kim MJ, Sharp JT et al (1988), Larson JL, Covey MK, Wirtz SE et al (1999), Lisboa C, Villafranca C, Leiva A et al (1997), Patessio A, Rampulla C, Fracchia C et al (1989), Preusser BA, Winningham ML, Clanton TL (1994), Villafranca C, Borzone G, Leiva A (1998), Wamke T, Formanek D, Lahrmann H et al (1994), Weiner P, Azgad Y, Ganam R (1992).</p>
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Author / Title / Reference / Yr	Puente-Maestu, L., Sanz, M. L., Sanz, P., Cubillo, J. M., Mayol, J., & Casaburi, R. 2000, "Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease. ", <i>European Respiratory Journal</i> , vol. 15, no. 3, pp. 517-525. Ref ID: 1228
N=	N=41. Location=Spain. Duration=8 wks
Research Design	Randomised, controlled, parallel two-group study.
Aim	To compare two-exercise training programmes, one fully supervised at the hospital, and the other self-monitored by the patient, in which participation of hospital staff was minimal.
Operational Definition	As per inclusion criteria (below)
Population	Males with severe COPD (excluding asthma)
Intervention and Comparison	One of two 8 wk training programmes: 1. Supervised training on a treadmill, 4 days (group S N=21) 2. Walking 3 or 4 km in 1h, 4 days week, self monitored with a pedometer, with weekly visits to encourage adherence (group SM, N=20)
Outcomes	Chronic respiratory diseases questionnaire (CRQ) and two exercise tests on a treadmill; incremental (IT) and constant (CT), above lactic threshold or 70% of maximal oxygen uptake ($\dot{V}O_2$, max) with arterial blood lactate determinations.
Characteristics	Inclusion criteria: Age <75yrs / severe COPD – post bronchodilator FEV1 <50% of predicted and FEV1/ FVC <0.7 without significant reversibility (<15% of the initial value, 15 min after the inhalation of 200ug of salbutamol) / stable COPD / grade 2 or more of dyspnoea MRC scale. Characteristics: Mean FEV1 1.09 +/-0.16 / 40.6 +/- 6.2% predicted / Mean age 64yrs / all males.
Results	CRQ There were no differences between the two groups either before or after training. All four dimensions of the CRQ improved significantly. Lung function and arterial blood gases

	<p>Little change in pulmonary function tests after training. Changes apparent in both groups, without significant differences between them.</p> <p>Supervised Training: Reconditioning yielded significant ($p < 0.05$) increases in $\dot{V}O_2$, max and increases in duration, with decreased lactate accumulation, ventilation, CO_2 output ($\dot{V}CO_2$), heart rate and diastolic blood pressure at the end of CT.</p> <p>Self Monitoring Training: Significant increases ($p < 0.05$) in duration, lower HR and DBP at the end of CT.</p> <p>Significantly ($p < 0.05$) different effects between Supervised and Self Monitoring programmes were (in favour of supervised group): Changes in $\dot{V}O_2$, max 100 +/- 101 ml/min⁻¹ versus 5 +/- 101 ml/min⁻¹, duration of the CT (8.1 +/- 4.4 min versus 3.9 +/- 4.7 min), $\dot{V}CO_2$ (-94 +/- 153 ml/min⁻¹ versus 48 +/- 252 ml/min⁻¹), lactate accumulation (-1.3 +/- 2.2 mmol/l⁻¹ versus 0 +/- 1.2 mmol/l⁻¹ and respiratory rate at the end of CT (-4.3 +/- 3.4 min⁻¹ versus -1 +/- 4.2 min⁻¹).</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
Source	Paper suggested by member of GDG
NCC CC ID	1228

Author / Title / Reference / Yr	Young, P., Dewse, M., Fergusson, W., & Kolbe, J. 1999, "Respiratory rehabilitation in chronic obstructive pulmonary disease: Predictors of nonadherence", <i>European Respiratory Journal</i> , vol. 13, no. 4, pp. 855-859. Ref ID: 1040
N=	N=91 Duration=4 wk COPD rehabilitation programme Location=New Zealand
Research Design	Cross sectional study.
Aim	The aim of the project was to determine whether persons who declined participation in or failed to complete a COPD rehabilitation programme differed significantly in terms of socio demographics, physiological parameters or psychological factors, from those who completed the programme.
Operational Definition	FEV1 <60% predicted, FEV1/FVC <65% and <20% improvement in FEV1 with inhaled bronchodilators.
Population	Moderate-to-severe COPD Classified following COPD rehabilitation programme into: 1. "Adherent" group who completed the total programme (N=55)

	2. "Non adherent" group who refused or began but did not complete the programme (N=36)															
Intervention	4 wk hospital based outpatient COPD rehabilitation programme conducted predominantly by respiratory physiotherapists															
Research Tool	All potential participants undertook an interviewer-administered questionnaire addressing social, economic, psychological and health care factors.															
Outcomes	Socio demographic variables / physiological parameters / psychosocial parameters															
Characteristics	Pts considered ineligible if they had severe co morbidity which significantly interfered with their ability to participate in the programme Age - >50yrs															
Results	<p>The non-adherent group were more likely to be widowed or divorced and less likely to be currently married ($p<0.001$), more likely to live alone (39% vs 14%, $p<0.02$), and more likely to live in rented accommodation (31 vs 6%, $p<0.002$). The non-adherent group were more likely to be current smokers (28 vs 8%, $p<0.02$).</p> <p>There was little difference in management of COPD between the two groups with similar proportions of the non adherent and adherent groups having previous specialist in put (92 and 88% respectively) and being on long term O2 therapy (8 and 12% respectively). Daily use of a peak flow meter was lower in the non-adherent group (18 vs 39%, $p=0.09$).</p> <p>Drug therapy was similar in the two groups (14 and 12%). However, the non adherent group were less likely to be using high doses ($>1,000\mu\text{g}$ of Beclomethasone dipropionate or equivalent) of inhaled corticosteroids (16 vs 42%, $p<0.005$)</p> <p>There were minimal differences between the two groups in baseline physiological variables and in any of the indices of COPD morbidity.</p> <p>With regard to differences in baseline psychosocial parameters and QOL domains between the two groups, the incidence of clinically significant depression (6 vs 0%, $p=0.09$), previous emotional counselling (25 vs 16%), hyperventilation (28 vs 22%) and inadequate social support for emotional problems (33 vs 20%, $p=0.14$) are higher in the non adherent group, these differences do not reach statistical significance.</p> <p>Inadequate social support for COPD related problems (51 vs 2%, $p=0.001$) was more common in the non-adherent group.</p> <p>Odds ratio and 95% confidence intervals (CI) for predicting adherence with respiratory rehabilitation programme for COPD.</p> <table border="1"> <thead> <tr> <th><i>Variable</i></th> <th><i>Odds ratio</i></th> <th><i>95% CI</i></th> </tr> </thead> <tbody> <tr> <td>Married</td> <td>7.2</td> <td>2.8 – 18.5</td> </tr> <tr> <td>Current smoker</td> <td>0.3</td> <td>0.1 – 0.9</td> </tr> <tr> <td>Own house</td> <td>7.7</td> <td>2.0 – 29.7</td> </tr> <tr> <td>Lack of COPD social support</td> <td>0.1</td> <td>0.0 – 0.3</td> </tr> </tbody> </table> <p>If the risk factors of current smoking, being divorced or widowed and lack of COPD related social support are considered, any two</p>	<i>Variable</i>	<i>Odds ratio</i>	<i>95% CI</i>	Married	7.2	2.8 – 18.5	Current smoker	0.3	0.1 – 0.9	Own house	7.7	2.0 – 29.7	Lack of COPD social support	0.1	0.0 – 0.3
<i>Variable</i>	<i>Odds ratio</i>	<i>95% CI</i>														
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Own house	7.7	2.0 – 29.7														
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	factors were found in 33% of the non adherent group but in none of the adherent group (p=0.01) while any one factor in 53% of the non adherent group and 20% of the adherent group (p=0.015). Hence facts strongly associated with non-adherence were current smoking, being widowed or divorced, living alone or lacking COPD disease-specific social support.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	III
NCC CC ID	1040

Author / Title / Reference / Yr	Foglio, K., Bianchi, L., & Ambrosino, N. 2001, "Is it really useful to repeat outpatient pulmonary rehabilitation programs in patients with chronic airway obstruction? A 2-year controlled study", <i>Chest</i> , vol. 119, no. 6, pp. 1696-1704. Ref ID: 1045
N=	N=61 Duration=1yr after completing 8 wk outpatient pulmonary rehabilitation program. Location=Italy
Research Design	The participants in this study had participated in a previous observational study, which evaluated the long-term effectiveness of pulmonary rehabilitation (Foglio et al 1999). This RCT was designed for those pts completing the 1999 program. All participants had completed a pulmonary rehabilitation program (PRP1). N=61 were randomised into two groups. Group 1 = completed a second pulmonary rehabilitation program (PRP2) 1 yr following the first PRP1 Group 2 = acted as the control and did not received any intervention At two years both group 1 and group 2 received pulmonary rehabilitation (known as PRP3)
Aim	<ol style="list-style-type: none"> 1. Can pulmonary rehabilitation lead to similar short term gains at successive, yearly interventions 2. Is there any real clinical or physiological long-term benefit by yearly repetition of pulmonary rehabilitation programs (PRPs)?
Operational Definition	Diagnosis of COPD was made according to the ATS guidelines. Asthma was defined as variable airflow limitation with reversible obstruction (range 12-15%, mean +/- SD 28 +/- 10%). Day hospital based pulmonary rehabilitation included exercise training, education and psychosocial support. Duration of program not detailed.
Population	CAO (26 COPD, 35 asthma)
Intervention	At 1 year following completion of PRP1, group 1 completed a second PRP (PRP2).
Comparison	At 1 year following completion of PRP1, group 2 received no intervention. (Control)
	One year later, both groups performed a third PRP (PRP3).
Outcomes	Lung function, cycloergometry, walking test, dyspnoea, HRQL assessed before and after PRP2 and before and after PRP3. The numbers of hospitalisations and exacerbations over the year were also recorded.

Characteristics	Concomitant medications – Asthmatic pts received inhaled steroids and bronchodilators, whereas all COPD pts received regular treatment with inhaled bronchodilators. No COPD pts received regular treatment with inhaled or oral steroids. Age, sex & FEV1 % predicted – Split for 8 groups, no overall total or range given. Ethnic origin not given.
Results	<p>Lung & Respiratory Function There was no significant change over time for lung & respiratory muscle function in either group.</p> <p>Exercise Tolerance (6MWD and cycloergometry peak workload) Following PRP2 intervention / control period, exercise tolerance increased in the PRP 2 group. However, this benefit was lost again such that exercise tolerance in pts of group1 was not significantly different from control subjects who did not attend any other PRP but PRP1. PRP3 resulted in a new improvement in exercise tolerance for both groups (p<0.05)</p> <p>Dyspnoea (BDI and TDI) Each PRP was followed by an improvement in the TDI, but no difference was observed between the two groups at any time in either index.</p> <p>Quality of Life (SGRQ) One year later, pts of group 1 did not differ from pts of group 2 in any outcome parameter, such that in comparison to before PRP1, only HRQL was still better <i>in both groups</i> 24 months after PRP1.</p> <p>Hospitalisation & Exacerbations Yearly hospitalisations and exacerbations per pt significantly decreased in both groups in the 2 yrs following PRP1, when compared to the 2 yrs prior. At the 24 month follow up visit, a further reduction in yearly exacerbations was observed only in group 1 but not in group 2 in comparison to what was observed at the 12 month follow up visit. NB which component of the program influenced this result is not clear.</p> <p>Mortality No patients died during the study.</p>
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1045

Author / Title / Reference / Yr	Roomi, J., Johnson, M. M., Waters, K., Yohannes, A., Helm, A., & Connolly, M. J. 1996, "Respiratory rehabilitation, exercise capacity and quality of life in chronic airways disease in old age", <i>Age and Ageing</i> , vol. 25, no. 1, pp. 12-16. Ref ID: 1226
N=	N=15. Location=England. Duration 12 wks of incremental respiratory rehabilitation.
Research Design	Case-control study for 6-minute walk distance only. Subjects with aged matched controls.

	Observational study (excluding above component).
Aim	Aimed to: a) assess repeatability of the 6 minute walk test, factors affecting it and its relation to quality of life in elderly pts with chronic obstructive airways disease; b) assess compliance of such pts with an intensive respiratory rehabilitation protocol; c) pilot the assessment of the effect of respiratory rehabilitation on the 6-minute walk test in these pts.
Operational Definition	FEV1 less than 60% of predicted, FEV1/FVC ratio less than 60% and less than 15% increase in FEV1 after 5 mg nebulised salbutamol.
Case Population	Elderly pts with COAD (aged 70-89 yrs, mean age 76yrs).
Control Population	Aged matched ambulant, community dwelling controls with normal respiratory function were recruited for a baseline 6-minute walk distance only. (Providing comparative data on 6-minute walk distances for normal elderly persons).
Intervention	Pts attended the geriatrics day hospital for 14 wks. They received 12 wks incremental respiratory rehabilitation (x4 / day step-ups, un weighted arm raises, inflating balloons).
Outcomes	Lung function / 6-minute walk test / Guyatt respiratory questionnaire
Characteristics	Subjects N=15 - Males N=6 / Mean (standard deviation) FEV1=49 (5)% predicted. / Mean age 76yrs / Co morbidity includes ischaemic heart disease, controlled left ventricular failure, peripheral vascular disease, osteoarthritis of knees, Parkinson's disease, symptomatic spinal osteoporosis. Controls N=25 - Males N=12 / Mean age 77yrs.
Results	The 95% confidence limits for repeat 6-minute walking distance in the subject group were -62.35m to 63.65m. Mean (SEM) 6-minute walk distance for controls was 409 (13.9)m. Baseline 6 minute walk was repeatable and was correlated with log Guyatt dyspnoea score (r=0.65, p=0.006). Multiple regression demonstrated that neither age nor FEV1 predicted walk distance, but the following were independent predictors of pre-programme 6-minute walk distance; maximal expiratory mouth pressure (t=2.54, p=0.039); calorie intake (t=2.52, p=0.040) and (negatively) body mass index (t= -3.1, p=0.018). Mean (SEM) 6-minute walk distance after rehabilitation was greater than baseline (p=0.003).
SIGN Quality Rating	+ (Note small sample size and study design limitations – treat with caution)
Hierarchy of Evidence Grading	11b
Source	Paper suggested by member of GDG
NCC CC ID	1226

Author / Title / Reference / Yr	Wijkstra, P. J., TenVergert, E. M., van, A., Otten, V., Kraan, J., Postma, D. S., & Koeter, G. H. 1995, "Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease", <i>Thorax</i> , vol. 50, no. 8, pp. 824-828. Ref ID: 1030
N=	N=36 Location=Netherlands
Research Design	RCT
Aim	To assess the long term effects of 1/12 physiotherapy vs once weekly physiotherapy at home after a comprehensive home rehabilitation program.
Operational Definition	COPD defined as per ATS criteria
Population	Severe airways obstruction (FEV1 <60% predicted and FEV1/IVC <50% after bronchodilator)
Intervention & Comparison	Group A & B started a rehabilitation program for 18 months During the first 12 wks, both group A&B were visited by a physiotherapist twice week for a session of 0.5 hrs. Pts were also coached 1/12 by both GP & nurse. After 12 wks: Group A visited the physiotherapist for a weekly 0.5 hr session N=11 Group B had a monthly session of 0.5hr N=12 Group C received no rehabilitation at all N=13
Outcomes	Measures were recorded at baseline, 3, 6, 12 & 18 months. QoL / Exercise Tolerance / Lung Function
Characteristics	Mean age – 63yrs / 83% males / Mean (SD) FEV1 1.3 (0.4) L, FEV1/inspiratory vital capacity 37.2 (7.9%)
Results	Lung Function Analyses within the groups showed a significant (p<0.05) decrease in FEV1 in group B at 3/12 compared with the baseline value. There were no other FEV1 significant differences. IVC in group C (control group), decreased significantly at 3, 12, and 18 months compared with the baseline. QoL Only group B had significantly higher scores for all dimensions at all time points compared with the baseline values. In addition, the sum score for quality of life in both groups A & B was higher at all time points compared with their baseline value, and reached significance (p<0.05) in only group B at all time points. Six Minute Walking Distance The 6 minute walking distance of group C (control) decreased significantly at 12 & 18 months compared with the baseline value, while no changes were seen in groups A & B.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b

NCC CC ID	1030
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Author / Title / Reference / Yr	Wijkstra, P. J., van, d., Kraan, J., van, A., KOETER, G. H., & POSTMA, D. S. 1996, "Effects of home rehabilitation on physical performance in patients with chronic obstructive pulmonary disease (COPD)", <i>European Respiratory Journal</i> , vol. 9, no. 1, pp. 104-110. Ref ID: 1033
N=	N=43 Duration=12wks Location=Netherlands
Research Design	RCT
Aim	Investigated whether 12 wks of rehabilitation at home in pts with COPD had a beneficial effect on lactate production, metabolic gas exchange data, workload of the inspiratory muscles, and dyspnoea during a maximal bicycle ergometer test.
Operational Definition	COPD as per ATS criteria Two groups of 15 pts each started a rehabilitation programme for 18 months, whilst one group of 15 pts formed a control group. During the first 12 wks, both rehabilitation groups received the same programme. They then received a different follow-up of physiotherapy. The pts of both rehabilitation groups were pooled, since the effects of rehabilitation during the first 12 wks had been investigated. Pts carried out a home rehabilitation programme and were supervised by a multidisciplinary team. The physiotherapy programme consisted of relaxation exercises, breathing retraining, upper limb training, target flow inspiratory muscle training (IMT) and exercise training on a home trainer. In addition to the physical training, a nurse and GP supervised pts once a month.
Population	COPD with severe airways obstruction (Entry criteria FEV1 <60% predicted, FV1/IVC <50% after bronchodilator)
Intervention	12 wk home rehabilitation programme (N=28).
Comparison	No rehabilitation (N=15)
Outcomes	Exercise tolerance (6MWD and maximal workload (Wmax during cycle ergometer test)), inspiratory muscle workload (tension time index (TTI)) and dyspnoea at Wmax with Borg scale.
Characteristics	Concomitant medication included inhaled corticosteroids, inhaled anticholinergic and / or inhaled beta agonist Average age – 63yr / Sex – 86% male / Mean FEV1 1.3 L, 44% predicted, mean FEV1/IVC 37+/-8%
Results	Cycle ergometer test The rehabilitation group showed an improved Wmax (p<0.05) of 10% (from 70 to 78) after 12 wks. Wmax decreased by 9% in the control group, the difference between the two groups being significant (p<0.01). The symptom limited VO2 (VO2-SL) in the rehabilitation group was also significantly higher after 12 wks compared to the control group (p<0.05). The dyspnoea score of the rehabilitation group at Wmax was lower (p<0.01) after 12 wks compared to baseline; there was no significant difference from baseline in the control group.

	<p>The rehabilitation group showed a significant decrease in TTI both at rest ($p < 0.01$) and at W_{max} ($p < 0.05$) after 12 wks. This group had a decrease in maximal lactate production ($p < 0.05$) of 0.6 mEq.L^{-1} after 12 wks compared to baseline. Decreases in TTI and lactate were found at a significantly higher W_{max} compared to baseline (78 vs 70 W). The decrease in the TTI at W_{max} in the rehabilitation group was due to a decrease in the ratio tI/t_{tot} (from 0.38 to 0.33; $p < 0.05$) and an increase of sniff Poes from 8.0 to 8.4 kPa) and the ratio tI/t_{tot} (from 0.38 to 0.37) were not significant in the control group.</p> <p>Although both dyspnoea and TTI at W_{max} decreased in the rehabilitation group, the changes were not significantly correlated to each other. Minute ventilation measure after 12 wks at identical baseline workloads, showed a significant decrease in the rehabilitation group (from 31.8 (9.9) to 29.4 (9.6) L.min^{-1}; $p < 0.01$). In the control group there was a non-significant decrease in VE assessed at the same workload from 34.9 (9.0) to 32.4 (9.0) L.min^{-1}. Whilst only six pts from the control group reached their baseline W_{max}, 23 pts from the rehabilitation group reached their baseline W_{max}.</p> <p>Six minute walking distance</p> <p>The 6MWD increased significantly in the rehabilitation group from 438 (84) to 447 (87) m. In contrast, the control group showed a decrease from 472 (121) to 444 (141) m, the difference between the two groups being significant ($p < 0.05$).</p>
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1033

Author / Title / Reference / Yr	Troosters, T., Gosselink, R., & Decramer, M. 2000, "Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: A randomized trial", <i>American Journal of Medicine</i> , vol. 15 AUG00109, no. 3, p. pp-212. Ref ID: 1043
N=	N=100 Duration=6 months Location=Belgium
Research Design	RCT
Aim	Investigate short and long term effects of a 6/12 outpatient-training program as compared with usual care.
Operational Definition	FEV1 <65% predicted.
Population	Severe COPD
Intervention	Outpatient training program including cycling, walking and strength training (N=50)
Comparison	Usual care (N=50). Details of usual care not described.
Outcomes	Measurements were made at enrolment, 6 and 18 months. Pulmonary function, functional and maximal exercise capacity, peripheral and respiratory muscle strength and QoL. Cost effectiveness.

Characteristics	Concomitant medications – not detailed Age – Mean age in the control group = 63yrs / mean age in the training group 61 yrs. Sex – 90% male Ethnic origin – not detailed Mean FEV1 (% predicted) at baseline – Control group 43% / training group 41%
Results	Compared with usual care, there were no significant effects of the training program on measures of pulmonary function. At 6/12, the training group showed improvement in 6MWD (mean difference, training – control, of 52 m; 95% CI, 15 to 89m, maximal work load (12 W; 95% CI, 6 to 19W), maximal oxygen uptake (0.26 litres/min; 95% CI, 0.07 to 0.45 liters/min), quadriceps force (11 cm H ₂ O; 95% CI, 3 to 20 cm H ₂ O)) and QoL (14 points; 95% CI 6 to 21 points; all p<0.05). At 18 months all these differences persisted (p<0.05) except for inspiratory muscle strength. For 6MWD and QoL, the differences between the training group controls at 18 months exceeded the minimal clinically important difference.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
Source	Paper suggested by member of GDG
NCC CC ID	1043

Author / Title / Reference / Yr	Green, R. H., Singh, S. J., Williams, J., & Morgan, M. D. 2001, "A randomised controlled trial of four weeks versus seven weeks of pulmonary rehabilitation in chronic obstructive pulmonary disease", <i>Thorax</i> , vol. 56, pp. 143-145. Ref ID: 1047
N=	N=44 Location=UK
Research Design	RCT
Aim	To determine whether a shortened four wk programme would provide equal benefits to pts in terms of improvements in health status and exercise capacity as out the traditional seven wk pulmonary rehabilitation course.
Operational Definition	FEV1 <80%, ratio of FEV1 to forced vital capacity <70%
Population	COPD
Intervention	Standard 7-week twice-weekly outpatient based pulmonary rehabilitation programme (comprising of disease education and exercise training including aerobic walking, general mobility and strength training. The educational component comprised 14 sessions of discussions and practical demonstrations from a range of health care professionals.)
Comparison	Comparable but shortened four-week course (Identical to above but shortened training programme).

Outcomes	CRQ / Breathing Problems Questionnaire (BPQ) / the incremental shuttle walking test (SWT) / treadmill endurance test (TET)															
Characteristics	Age – Mean 69yrs / Sex – 61% male / Mean FEV1 at screening visit was 1.03 L for the 4wk group and 1.08 L for the 7wk group.															
Results	<p>There were clinically relevant differences in the baseline shuttle walking test distance and in the CRQ domains of fatigue, emotion and mastery. However the authors state that the analysis of covariance model allows for these inequalities and that a true difference between the two lengths of treatment is demonstrated by the outcome results:</p> <table border="0"> <thead> <tr> <th></th> <th>4wk group at baseline</th> <th>7wk group at baseline</th> </tr> </thead> <tbody> <tr> <td>SWT</td> <td>140.00 m</td> <td>187.6 m</td> </tr> <tr> <td>CRQ fatigue</td> <td>2.86</td> <td>3.42</td> </tr> <tr> <td>CRQ emotion</td> <td>3.64</td> <td>4.36</td> </tr> <tr> <td>CRQ mastery</td> <td>3.60</td> <td>4.34</td> </tr> </tbody> </table> <p>Outcome measures: Pts who completed the 7 wk rehabilitation programme had greater improvements in all outcome measure than those undertaking the four wk course. These differences reached clinical and statistical significance for the: Total CRQ score, mean difference –0.61, 95% CI –0.15 to –1.08, p<0.05 CRQ dyspnoea –0.80, 95% CI –0.13 to –1.48, p<0.05. CRQ emotion –0.89, 95% CI –0.33 to –1.45, p<0.005. CRQ mastery (-0.84, 95% CI –0.10 to –1.58, p<0.5</p> <p>There were no statistically significant differences in exercise assessment.</p>		4wk group at baseline	7wk group at baseline	SWT	140.00 m	187.6 m	CRQ fatigue	2.86	3.42	CRQ emotion	3.64	4.36	CRQ mastery	3.60	4.34
	4wk group at baseline	7wk group at baseline														
SWT	140.00 m	187.6 m														
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CRQ emotion	3.64	4.36														
CRQ mastery	3.60	4.34														
SIGN Quality Rating	-															
Hierarchy of Evidence Grading	1b															
NCC CC ID	1047															

Author / Title / Reference / Yr	Wedzicha, J. A., Bestall, J. C., Garrod, R., Garnham, R., Paul, E. A., & Jones, P. W. 1998, "Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale", <i>European Respiratory Journal</i> , vol. 12, no. 2, pp. 363-369. Ref ID: 222
N=	N=126 Duration=8wk programme. Location=UK. Setting: 1. Moderately dyspnoeic participant interventions were carried out in a hospital outpatient setting. 2. Severely dyspnoeic participant interventions were carried out at home.
Research Design	RCT

Aim	To investigate whether there is heterogeneity in the response to exercise training in severe COPD patients with different degrees of disability.
Operational Definition	FEV1 <70% predicted with <15% reversibility to inhaled salbutamol.
Population	COPD Participants were stratified according to the level of dyspnoea into moderately dyspnoeic and severely dyspnoeic groups
Intervention	Exercise plus education (exercise group)
Comparison	Education (control group)
Outcomes	Shuttle walking distance / exercise performance / health status.
Characteristics	70 males / 68 females / Median age 70 yrs (range 44 – 81)
Results	Statistically significant improvement in shuttle walking distance in the moderate dyspnoeic group who received exercise training, baseline 191 +/-22 m, post rehabilitation 279 +/- 22 m (p<0.001). There was no improvement in exercise performance in the severely dyspnoeic patients receiving exercise. Neither group of control patients improved. Health status, assessed by the CRDQ increased in the moderately dyspnoeic patients receiving exercised from 80+/-18 to 95 +/- 17 (p<0.0001) after rehabilitation. The moderately disabled control group and both treatment arms of the severely disabled group all showed smaller, but statistically significant improvements (p<0.05). There was no change in the EADL scores after rehabilitation in any group. There were no changes in spirometry or blood gases after the rehabilitation programmes in any of the four treatment groups.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
NCC CC ID	222

Author / Title / Reference / Yr	Lacasse, Y., Wong, E., Guyatt, G. H., King, D., Cook, D. J., & Goldstein, R. S. 1996, "Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease", <i>Lancet</i> , vol. 348, no. 9035, pp. 1115-1119. Ref ID: 235
N=	N=14 trials
Research Design	Meta analysis
Operational Definition	90% of pts had a clinical diagnosis of COPD and either a best-recorded ratio of FEV1 to FVC of less than 0.7 of a best-recorded FEV1 of less than 70% of the predicted value.
Population	COPD
Intervention	Inpatient. outpatient. or home based rehabilitation programme of at least 4wk duration that included exercise therapy with or without

	any form of education, psychological support for pts with exercise limitation attributable to COPD.
Comparison	No rehabilitation
Outcomes	Exercise capacity / Health related quality of life (HRQOL)
Characteristics	Age - Mean age range across 14 trials 61-75 yrs. Most had severe COPD Sex – Total male / female split not detailed (breakdown given for each trial) Ethnic origin – Not detailed
Results	<p>Maximum exercise capacity (11 trials, N=309 pts) The pooled effect size achieved significance (0.3 SD 95% CI; 0.1 – 0.6), which corresponded, in incremental cycle ergometer test units to 8.3 W (95% CI; 2.8 - 16.5). Homogeneity was found among study findings (p=0.85). This suggested that the effect of rehabilitation on maximum exercise capacity was constant across studies, irrespective of the duration or composition of the rehabilitation programme.</p> <p>Functional exercise capacity (11 trials, N=413 pts) Converting back to natural units for the 6-minute walk test (metre) the difference in response between the treatment and control group was 55.7 m (95% CI 27.8 – 92.8). The limits of the CI were wider than the estimated minimum clinically important difference (MCID) (37-71m). The effect of respiratory rehabilitation on functional exercise capacity favoured the treatment group with a pooled effect size of 0.6 SD (0.3 to 1.0). Heterogeneity among study results was apparent (p=0.0008) which could not be explained by subgroup analyses. Post hoc analysis showed a significant difference between programmes of 6/12 duration and the other programme (93m vs 39.2; difference, p=0.0004)</p> <p>HRQOL 12 of the 14 trials measured HRQOL and ten different instruments were used for the assessment. Evidence of validity and responsiveness for only two of the instruments has been published. Analysis of HRQOL was confined to the six trials in which one of these questionnaires was used.</p> <p>Dyspnoea (6 trials, N=234) Effect size 1.0 (0.6-1.5) p=0.12 Fatigue (4 trials, N=207) Effect size 0.6 (0.3-0.8) p=0.36 Emotional function (4 trials, N=207) Effect size 0.6 (0.2-1.0) p=0.68 Mastery (4 trials, N=207) Effect size 0.6 (0.4-0.9) p=0.77 For dyspnoea and mastery the overall <i>treatment effect</i> size was larger than the MCID: 1.0 (95% CI; 0.6-1.5) and 0.8 (95% CI; 0.5-1.2) respectively, compared with a MCID of 0.5</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a

NCC CC ID	235
Studies included	Mc Gavin 1977, Cockcroft 1981, Booker 1984, Jones 1985, Busch 1988, Lake 1990, Simpson 1992, Weiner 1992, Goldstein 1994, Reardon 1994, Vallet 1994, Wijkstra 1994, Guell 1995, Strijbos 1996.

Author / Title / Reference / Yr	Brooks, D., Krip, B., Mangovski-Alzamora, S., & Goldstein, R. S. 2002, "The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease", <i>European Respiratory Journal</i> , vol. 20, no. 1, pp. 20-29. Ref ID: 1051
N=	N=109 Duration=12 months Location=Canada
Research Design	RCT
Aim	Purpose of study was to examine the effects of two post rehabilitation programmes on functional exercise tolerance and health related quality of life
Operational Definition	Severe stable COPD (FEV1 <40% predicted, FEV1/FVC <0.7 Pulmonary rehabilitation program consisted of pt education, psychosocial support and supervised exercises, of which breathing exercises, interval training, upper extremity training, leisure walking and treadmill or cycle exercise comprised the main components. Outpatients exercised three times a wk at the centre and at home for 8 wks.
Population	Severe stable COPD. Pts from both inpatient and outpatient programmes
Intervention	Enhanced follow up (EF). Attended a monthly support group lead by a physical therapist and received a telephone call midpoint between their visits (2wks)
Comparison	Conventional Follow up (CF). Visited physical therapist every 3/12 for 1 yr. Asked standardised questions regarding illnesses or hospitalisations. If any parts of the programme had been discontinued, they were encouraged to resume them.
Outcomes	Functional exercise tolerance / HRQL / Measured at 3, 6, 9 and 12 months
Characteristics	Age – 49 to 85yrs / Sex – 59% male / Ethnic origin – not detailed / Mean FEV1 L 0.70, FEV1 32 % pred, FEV1/FVC 36.8 at baseline

Results	<p>Using time and group as factors, there was no difference in the distance walked in 6 min between the two groups (p=0.3), but a significant difference for time (p<0.001) and interaction between time and group (p=0.03). Post hoc analysis revealed that for the control group, distances walked at 6, 9 and 12 months were less than the distance at baseline (p<0.04). For the EF group, distance walked at 12 months was less than all other measure (p<0.001).</p> <p>There was no difference in total chronic respiratory disease questionnaire score between groups at baseline or at any time interval.</p> <p>Secondary outcomes measures:</p> <p>There was no difference between groups in the SF-36 for the domains of: social activities, pain, mental health, role activities and general health.</p> <p>There was no difference in the number of respiratory exacerbations between the groups.</p> <p>Pulmonary function did not change between groups.</p> <p>The number of participants who reported performing their exercises did not differ between the two groups (X² p=0.08) but deteriorated over time (p<0.001)</p> <p>Enhanced follow-up designed to promote programme adherence did not influence functional exercise capacity or HRQL 12 months post pulmonary rehabilitation. Although the walking distances improved among the study group at 6/12, HRQL did not and by 1 yr the groups did not differ in either outcome</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1051

Author / Title / Reference / Yr	Chavannes, N., Vollenberg, J. J. H., van Schayck, C. P., & Wouters, E. F. M. 2002, "Effects of physical activity in mild to moderate COPD: a systematic review", <i>British Journal of General Practice</i> pp. 574-578. Ref ID: 1230
N=	5 studies. Participants N=210
Research Design	Systematic Review (allowing inclusion for RCTs and cluster controlled trials only)
Aim	In general practice it is important that the advice given is clear, practical and acceptable to pts; characteristics that are not applicable to the complex, intensive, and exhaustive nature of pulmonary rehabilitation programmes. The authors questioned what evidence was available in literature regarding the efficacy of physical activity on functional status and prognosis in pts with mild to moderate COPD. A literature search was performed to find out whether physical activity has an influence on exercise tolerance, QoL and dyspnoea in pts with mild to moderate COPD and whether it influences the number of hospitalisation days and number of

	exacerbations, expressed as oral courses of prednisolone.
Operational Definition	Articles were excluded if they did not deal with the relationship between physical activity and COPD, only dealt with the training of highly specific muscle groups, only included severe COPD or if they were studies comparing two training programmes without control.
Population	Mild to moderate COPD (excluded severe COPD which was defined as FEV1 of 50% lower than predicted)
Intervention	Physical activity (general physical condition enhancement; e.g. walking, cycling, swimming or training of large muscle groups).
Comparison	A control group without intervention of physical activity
Outcomes	Exercise tolerance, QoL, dyspnoea, hospitalisations days and number of exacerbations, expressed as oral courses of Prednisolone.
Characteristics	Demographics not provided.
Results	<p>“Most of the studies showed significant differences between intervention and control groups with regard to exercise tolerance”. Diagram displaying random effects meta-analysis of physical activity on exercise tolerance (effect size and standard error given for each study only). No numerical representation of confidence intervals or overall meta analysis. No p values given. Although a meta analysis is provided summarising the effects on exercise tolerance, the numbers were small and different outcomes had to be integrated to produce the figure (this is acknowledged by the authors) hence no real conclusion can be drawn.</p> <p>The effects of physical activity on QoL in pts with mild to moderate COPD were inconclusive. The two studies involved used different instruments to assess QoL.</p> <p>No consistent effect was found on dyspnoea.</p> <p>None of the studies used numbers of hospitalisation days or prednisolone courses as outcome measurements.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
Source	Paper suggested by member of GDG
NCC CC ID	1230
Studies included	Cambach et al 1997 (N=23), Clark et al 1996 (N=48), Clark et al 2000 (N=43), Grosbois et al 1999 (N=58) and Ringbaek et al 2000 (N=38).

Author / Title / Reference / Yr	Strijbos, J. H., Postma, D. S., vanAltena, R., Gimeno, F., & Koeter, G. H. 1996, "A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD - A follow-up of 18 months", <i>Chest</i> , vol. 109, no. 2, pp. 366-372. Ref ID: 236
N=	N=41 pts (completed 18 months) Duration=12 wks of rehabilitation and 18 months of follow-up. Location=Netherlands
Research Design	RCT. Stratification for FEV1 and exercise tolerance, as measured by the walking distance.
Aim	The effects of hospital based outpatient pulmonary rehabilitation program (HRP) are compared with those of home-care rehabilitation program (HCRP) in COPD patients.
Operational Definition	Pa CO2 at rest of less than 6.5 kPa, and PaO2 at rest of more than 7.5 kPa; FEV1 post bronchodilatation between 600 and 1800 ml and less than 65% of predicted FEV1
Population	Moderate to severe stable COPD
Interventions	<p>Hospital based outpatient pulmonary rehabilitation (N=18) – Pts came to the hospital twice a wk during 12 consecutive wks. The rehabilitation exercise took 1 h each session and was administered by a physiotherapist. Pts were instructed to practice daily exercises individually for at least 15 min. Pt education was given three times by a respiratory nurse during 1hr each. All pts visited the physician three times.</p> <p>Home care rehabilitation (N=17) – The program for each patient was carried out at home by the local physiotherapist and home care nurse under supervision of the GP. The local physiotherapist administered the individualised exercise programs during 24 sessions of 30 min in 12 consecutive wks. Pts were instructed to exercise individually at least 30 min on the exercise days and at least 15 min on the other days. In addition, each pt was visited three times by the local home care nurse, who checked the use of medication, daily peak flow and motivated the pt to continue the exercises at home. All pts visited the GP on three occasions during the 12 wks of rehabilitation.</p> <p>The rehabilitation program consisted of the following components: Patient education / Breathing and relaxation exercises / Bronchial Hygiene / Exercise Reconditioning</p>
Comparisons	Control group (N=15) received no rehabilitation therapy they received standard medical treatment only.
Outcomes	Lung function / exercise performance (4 minute walking test and cycle ergometer test), dyspnoea, leg effort during exercise and well-being.
Characteristics	Airflow limitation (mean [SD] FEV1 % predicted, 42.8 [8.4]). Average age 61yrs 60% used three or more different drugs for maintenance treatment. N=43 male
Results	<p>All pts were followed up for 18 months with five visits to the hospital, at the start of the study, directly after finishing the rehabilitation program (after 3/12 and 6, 12 and 18 months after the start of the program).</p> <p>Exercise Test Maximal Work Level (W max, Cycle Test) – Significantly different responses were observed among all groups (p=0.001).</p>

	<p>After the hospital rehabilitation program at 3 months, a significant increase in W max of 20% was observed. However, throughout the follow-up period, W max deteriorated: at 12 and 18 months, no significant improvement was seen. After the home care rehab however, an ongoing gradual improvement was observed throughout the complete follow-up period. 18 months after the start of the study, W max was still 21% above baseline. Values at all follow up visits were significantly improved as compared with baseline after 12 and 18 months and also as compared with the control group. Improvements in W max at follow up were better maintained after the home care program (p=0.014).</p> <p>4 Min Walking Distance – In both therapy groups a significant increase in walking distance was measured after the rehabilitation programs (p=0.001). In the hospital group, distance covered in 4 min was significantly increased up to 6/12 compared with baseline. After the homecare rehab, walking distance was significantly increased at all follow-up visits, up to 14% at the last visit after 18 months. No significant differences were observed among the three groups at separate follow-up visits.</p> <p>Borg Scores During Cycle Test – Dyspnoea scores and scores for leg effort (Borg scale) at W max1 did not change significantly over 18 months in both therapy groups. Significantly different responses among the three groups were observed for both dyspnoea and leg effort scores at similar work levels (W max2 p=0.004 and p=0.04 respectively). In the hospital outpatient rehabilitation group similar work levels were attained with decreased dyspnoea scores up to 6 months after the start of the study. The score fore leg effort at these work levels showed only a significant improvement directly after the program at t3 months. In the home care rehabilitation group significant improvements in dyspnoea scores were maintained up to 18 months and for leg effort up to 6 months. Improvements in dyspnoea scores were significantly better maintained at follow up after home care rehabilitation as compared with outpatient rehabilitation, whereas no significant differences for leg effort scores were observed between the two therapy groups.</p> <p>Exercise Parameter during Cycle Test – No significant differences in heart frequency or SaO2.</p> <p>General Well-Being – Significant improvements in general well-being were observed in both rehabilitation groups, directly after the program and at follow-up after 18 months. In both rehab groups, a major proportion claimed an improved well-being directly after the program (12/15, p<0.01) and 11/15, p<0.05 respectively). After 18 months, most patient (13/14) in the control group felt unchanged or even worse.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	236

Author / Title / Reference / Yr	Troosters, T., Gosselink, R., & Decramer, M. 2001, "Exercise training in COPD: how to distinguish responders from nonresponders.", <i>Journal of Cardiopulmonary Rehabilitation</i> , vol. 21, no. 1, pp. 10-17. Ref ID: 1224
N=	N=49 pts evaluated. Location=Belgium. Duration 12 wks of exercise training.
Research Design	Observational. Before and after study.

Aim	Purpose of the trial was to investigate whether responders to an exercise-training program could be discriminated from non-responders based on pre training physiological variables.
Operational Definition	“FEV ₁ 37 (15) % pred”
Population	Moderate to severe COPD
Methods	49 stable outpatients with COPD were evaluated before and after 12 wks of exercise training (3 times per week). Responders in exercise capacity were defined as having 15% increase in maximal workload and / or 25% increase in walking distance, while responders in QoL showed an improvement of at least 10 points on the CRD questionnaire. With multivariate discriminant analysis, responders were distinguished from non-responders based upon their initial characteristics.
Outcomes	Measurement of pulmonary function, peripheral and respiratory muscle strength, exercise capacity & QoL.
Characteristics	Pts performed testing at inclusion and after 3/12 of outpatient pulmonary rehabilitation. During this period, all pts continued their medical treatment.
Results	N=32 pts (65%) met the criteria of responders in terms of improved exercise capacity. Ventilatory reserve, inspiratory muscle strength (PImax) (p<0.05) and peripheral muscle strength (handgrip force (p<0.01) and quadriceps strength (p<0.05)), and a measure of ventilatory limitation (VE/MVV, p<0.05) were significant predictors of the training response. No physiologic variables predicted whether a patient would increase quality of life after exercise training.
SIGN Quality Rating	No SIGN Checklist available for observational before and after design.
Hierarchy of Evidence Grading	III
NCC CC ID	1224

Author / Title / Reference / Yr	Berry, M. J., Rejeski, W. J., Adair, N. E., Ettinger, W. H., Zaccaro, D. J., Sevick, M. A. (2003). A randomized controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. <i>Journal of Cardiopulmonary Rehabilitation</i> , 23, 60-68.
N=	N=140; 84.3% (N=118) are included in the analysis. Short-term programme N=70/Long term programme N=70 Location= Wake Forest University, USA Sites=1 site
Research Design	A single centre, single blind, controlled randomised clinical trial.
Aim	To compare the effects of short-term (3 months) and long-term (18 months) participation in an exercise program on self-reported disability

Operational Definition	An expiratory airflow limitation that was not reversible with bronchodilator inhalation such that the ratio of the one second forced expiratory volume (FEV1) to the forced vital capacity (FVC) was less than or equal to 70% and the FEV1 was greater than or equal to 20% predicted.
Population	COPD patients who reported difficulties in performing activities of daily living.
Intervention	Short-term exercise programme (3-months 3x weekly for 1 hour supervised based-based program at Wake Forest University) N=56
Comparison	Long term exercise programme (18-months= 3-months 3x weekly for 1 hour followed by 15-months 3x weekly supervised centre-based program at Wake Forest University) N=62
Outcome	<p>Primary outcome measures</p> <ul style="list-style-type: none"> • Self-reported physical disability Fitness Arthritis and Seniors Trial functional performance inventory. The instrument assesses difficulty in performing activities of daily living. • Physical function Distance walked in 6 minutes; time to complete an overhead task; and time to climb two flights of stairs. <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Peak oxygen uptake Medical Graphics Corporation CPX-D (St. Paul, Minn) gas exchange system and a modified Naughton protocol with 2-minute stages. The graded exercise test was performed in the morning before the use of any bronchodilators. • Pulmonary function test These were performed according to ATS guidelines using a Medical Graphics Corporation 1085D plethysmograph. • Physical activity scale for the elderly Physical Activity Scale for the Elderly (PASE) which has been shown to be a valid measure of physical activity in older individuals, was used to assess physical activity levels in all participants
Characteristics	<p>ST=short term/LT=long term ST Gender M/F=39/31 LT Gender M/F=39/31 Mean age ST/LT=66.9yrs/68.4yrs Mean weight kg ST/LT=80.9/77.2 FEV1 ST/LT=1.65/1.52 FEV1 (% pred) ST/LT=59.1/57.6 FEV1/FVC (%) ST/LT=56.4/52.3 RV/TLC (%) ST/LT=55/57</p>
Results	<p>Primary outcome measure</p> <ul style="list-style-type: none"> • Self-reported physical disability

	<p>At 18-months participants in the long-term group reported approximately 12% less disability than those in the short-term group. The adjusted means (95% CI) were 1.53 (1.43 to 1.63) and 1.71 (1.61 to 1.81) units respectively p=0.016.</p> <ul style="list-style-type: none"> • Physical function At the 18-month assessment, participants in the long-term intervention walked more than 100 feet further in 6 minutes than those in the short-term intervention group (p=0.03). <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Peak oxygen uptake At 18-months there was no significant difference between long term and short term intervention groups. • Pulmonary function test No significant difference was found between the two intervention groups on pulmonary function tests. • Physical activity scale for the elderly No significant difference was found between the two intervention groups on PASE scores. <p>Those with higher compliance rates had better scores on self-reported disability and physical performance.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	Ib

Author / Title / Reference / Yr	Salman, G. F., Mosier, M. C., Beasley, B. W., Calkins, D. R. (2003). Rehabilitation for patients with chronic obstructive pulmonary disease: Meta-analysis of randomised controlled trials. J Gen Intern Med, 18, 213-221.
N=	N=20 trials (N=979 participants) Location=USA Sites=multiple-systematic review
Research Design	Meta-analysis: RCTs
Aim	To assess the effect of rehabilitation on exercise capacity and shortness of breath in patients with COPD, and to determine the optimal type and duration of rehabilitation programs.
Operational Definition	COPD was defined as forced expiratory volume in one second (FEV1) <70% predicted value or FEV1 Divided by forced vital capacity (FEV1/FVC) <70% predicted value.

Population	Adult mild/moderate and severe COPD
Intervention	Any type of rehabilitation (upper-extremity, lower-extremity, or respiratory muscle exercise) 3 times a week for at least 4 weeks.
Comparison	Control- no rehabilitation
Outcome	<ul style="list-style-type: none"> • <u>Exercise capacity</u> measured by the walking test. • <u>Shortness of breath</u> measured by the Chronic Respiratory Disease Questionnaire
Characteristics	<p><u>Mild/moderate COPD</u> N range: 14-200 Age range: 59yrs-71yrs Average FEV1 values >35% or 0.8L</p> <p><u>Severe COPD</u> Average FEV1 values <35% or 0.8L. N range: 14-77 Age range: 63yrs-72.5yrs</p> <p>There were no significant differences between the number of patients who dropped out of the rehabilitation groups and the number of patients who dropped out of the control groups (p=0.639).</p>
Results	<ul style="list-style-type: none"> • <u>Walking test</u> Pooled analysis (N=20 trials; N=979 participants) showed that the rehabilitation groups did significantly better (p<0.001) than control groups on the walking test. Subgroup analysis showed that the rehabilitation groups of trials that included mild/moderate COPD patients (<0.001) and trials that included severe COPD patients (p=0.005) did significantly better than control groups. • <u>Shortness of breath</u> Pooled analysis (N=12 trials; N=723 participants) showed that the rehabilitation groups were significantly less (p<0.001) short of breath than were control groups. Subgroup analyses showed that the rehabilitation groups of the trials that included mild/moderate COPD patients (p<0.001) and trials that included severe COPD patients (p=0.155) were both significantly less short of breath than were control groups. • <u>Exercise capacity</u> The rehabilitation groups in the trials that included at least lower-extremity training (N=18 trials) did significantly better (p<0.005) than control groups on the walking test. In the trials that included respiratory muscle training only (N=2 trials), there was no significant difference between rehabilitation and control groups. In the trials that included severe COPD patients, the rehabilitation groups did significantly better than control groups only when the rehabilitation programs were 6 months (p<0.005; N=4 trials) or longer. The rehabilitation groups of the trials that included patients with mild/moderate COPD did significantly better than control

	<p>groups with both long (p=0.018; N=2 trials) and short-term (p=0.020; N=10 trials) rehabilitation programs.</p> <ul style="list-style-type: none"> • <u>Shortness of breath</u> <p>Trials that included at least lower-extremity training (N=11 trials) were significantly less (P=0.063) short of breath than were the control groups. One trial that included respiratory muscle training only showed that there was no significant difference in shortness of breath between rehabilitation and control groups.</p> <p>In trials that included severe COPD, the rehabilitation groups experienced less (p=0.742) shortness of breath than did control groups only when the rehabilitation programs were 6 months or longer (N=2 trials).</p> <p>Rehabilitation groups of the trials that included patients with mild/moderate COPD were less short of breath than were control groups in both long (p=0.391; N=2 trials) and short-term (p=0.386; N=6 trials) rehabilitation programs.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	Ia
Included Studies	Lake (1990) N=14; Gosselink (1996) N=19; Wijkstra (1995) N=36; Simpson (1992) N=28; Guyatt (1993) N=82; Strijbos (1996) N=30; McGavin (1977) N=24; Cambach (1997) N=19; Cockcroft (1981) N=34; Bendstrup (1997) N=32; Sassi-Dambon (1995) N=77; Griffith (2000) N=200; Wedzicha (1998) N=56; Troosters (2000) N=62; Bauldoff (1996) N=20; Weiner (1992) N=24; Goldstein (1994) N=77; Jones (1985) N=14; Engstrom (1999) N=50; Wedzicha (1998) N=54; Guell, (2000) N=47.
NCC CC ID	19351

Author / Title / Reference / Yr	Ortega, F., Toral, J., Cejudo, P., Villagomez, R., Sanchez, H., Castillo, J., Montemayor, T. (2002). Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 166, 669-674.
N=	N=47 participants Location= Sevilla, Spain Sites= 1 site Duration 3/12
Research Design	Prospective comparative follow-up study: pre-training, end of 12 week training, 12 weeks after training.
Aim	To compare the efficacy of endurance, strength, and the combination of strength and endurance training in patients with COPD. To assess the outcome of the training intervention after 3 months.
Operational Definition	The diagnosis of COPD was based on smoking history and on pulmonary function tests showing irreversible bronchial obstruction defined by less than 12% and less than a 200-ml increase of initial FEV1 after administration of salbutamol (400 ug via a metered dose inhaler).
Population	Patients with moderate to severe COPD.
Intervention	Strength training N=17 Endurance training N=16 Strength + endurance training N=14
Comparison	No comparison to standard care- the groups are compared to other interventions- as above.
Outcome	<ul style="list-style-type: none"> • Pulmonary function and peak exercise parameters- VO_{2max} (L/min); VO_{2max} (% predicted); W_{max} (W); W_{max} (% predicted); V_{emax} (L/min). • Exercise capacity- shuttle walking test, endurance test, strength measurements (kg; chest pull; butterfly; neck press; leg flexion; leg extension. • Changes in Baseline Dyspnea Index and Chronic Respiratory Questionnaire
Characteristics	ST=strength training/ET=endurance training/SE=strength+endurance Mean age ST/ET/SE=66yrs/66yrs/60yrs Sex M/F: ST=14/3; ET=14/2; SE=13/1 FVCL ST/ET/SE = 2.54/2.50/2.38 FVC % predicted ST/ET/SE = 72/71/67 FEV1L ST/ET/SE = 1.12/1.13/0.93

	FEV1% predicted ST/ET/SE =40/41/33 FRC% ST/ET/SE =161/172/173 TLC% ST/ET/SE = 113/120/117
Results	<p>Pulmonary function and peak exercise parameters- VO_{2max} (L/min); VO_{2max} (% predicted); W_{max} (W); W_{max} (% predicted); V_{emax} (L/min).</p> <p>No significant changes in pulmonary function tests were seen in any of the groups.</p> <p>Exercise capacity- shuttle walking test, endurance test</p> <p>The improvement in the shuttle-walking test was only statistically significant in the strength-training group (p<0.015). Comparisons between the three study groups were not significant either both at the end of the 12-week training period and at 12-weeks after training.</p> <p>At the end of the training period and at 12 weeks after training, all patients in the three groups showed significant increases in the duration of endurance testing as compared with pre-training values. However, increases in pre-training vs end of 12-week training obtained in the endurance group were significantly higher than those observed in the strength group (P<0.001) but were of similar magnitude than those in the combined training group, which in turn were significantly higher (p<0.017) than those in the strength group. However, between-group comparisons of decreases observed at the post-training assessment as compared with end of 12-week training were not significant.</p> <p>Strength measurements (kg; chest pull; butterfly; neck press; leg flexion; leg extension</p> <p>At the end of the training period and at 12 weeks after training, all patients in the three groups showed statistically significant increases in the strength of the muscle groups measured in the five exercises. In the endurance group, increases in the strength measures involving the upper extremities were lower compared with increases in the strength measures involving the lower extremities. Increases in pre-training vs the end of 12-week training obtained in the strength group were significantly higher than those observed in the endurance group but were of similar magnitude to those in the combined training group, which in turn showed significantly higher increases than subjects in the endurance-training group.</p> <p>There were no statistically significant in the increases in muscle strength between the strength training modality and the combined group except for butterfly (p<0.017).</p> <p>Decreases in muscle strength observed at 12 weeks after training as compared with the end 12-week training were significantly greater in the strength group as compared with the endurance group for chest pull, butterfly, leg flexion. That reduction in peripheral muscle strength of the combined group, with no significant differences existing between them.</p> <ul style="list-style-type: none"> • Changes in Baseline Dyspnea Index and Chronic Respiratory Questionnaire <p>The strength group showed significant improvements in both fatigue and emotion, whereas statistically significant improvements were observed only in the dimension of fatigue for the endurance group and in the dimension of emotion for the combined modality group.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	III

NCC CC ID	19373
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Author / Title / Reference / Yr	Bestall, J. C., Garrod, P. R., Garnham, R., Jones, P. W., Wedzicha, J. A. (2003). Longitudinal trends in exercise capacity and health status after pulmonary rehabilitation in patients with COPD. <i>Respiratory Medicine</i> , 97, 173-180.
N=	N=128 participants Location = Respiratory out-patient clinic at the London Chest Hospital, UK Sites = 1
Research Design	RCT randomised controlled, 6 month and 1 year follow-up trial
Aim	To assess the long-term effect of pulmonary rehabilitation in patients with moderately disabling COPD that had received an 8 week training programme.
Operational Definition	COPD- forced expiratory volume in Is (FEV1) less than 15% reversibility to inhaled salbutamol (400mcg). Moderate dyspnoea as defined by the MRC Dyspnoea Scale
Population	COPD patients with moderate dyspnoea Inclusion criteria: <ul style="list-style-type: none"> History of COPD with forced expiratory volume in Is (FEV1) less than 15% reversibility to inhaled salbutamol (400mcg). Exclusion criteria: <ul style="list-style-type: none"> Patients with unstable angina, peripheral vascular disease, joint limiting mobility condition; Patients who were unable to understand and complete questionnaires
Intervention	Exercise training group Exercise training group received both exercise and education twice weekly for 8 weeks.
Comparison	Education group (control) Education group received education twice weekly for 8 weeks.
Outcome	Primary outcome measure Shuttle walking test Secondary outcome measure Health status
Characteristics	Total Group Median age (yrs)= 70 (range 44-81) N males/females= 70/68

	<p>Exercise/Control Group Age (years) Exercise/control =68.2/69.2 FEV1(l) exercise/control=0.93/1.00 FEV1% predicted exercise/control=37/38 FVC (l) exercise/control=2.60/2.52 PaO₂ (kPa) exercise/control=8.99/8.62 PaCO₂ (kPa) exercise/control=5.80/5.75 Shuttle (m) exercise/control=195/220 SGRQ total exercise/control=51.0/51.9 CRQ total exercise/control=79.9/85.6 HAD depression exercise/control=4.5/4.6 EADL exercise/control=18/18</p>
<p>Results</p>	<p><i>Primary outcome measure</i> Shuttle Walking Distance <i>Exercise tolerance 1 year compared to post-rehabilitation</i> There was a steady decline in SWD during the follow-up period ($F_{1,44}=15.97$, $p<0.0001$). The exercise group had a mean (95%) decline of -60 (-31 to -90)m and the control group declined by a mean (95%CI) of -23(-5 to 52)m from 8 weeks to 1 year.</p> <p>Exercise tolerance after 1 year compared to baseline There was a significant difference between SWD measured at baseline and 1 year between the two groups (main effect $F_{1,43}=6.42$, $p=0.015$). The exercise group had a mean (95% CI) increase of 28 (-9 to 65)m whereas the control group had a mean (95% CI) decline of -40(-3 to 84)m. The changes within groups were not statistically different.</p> <p>Lung Function There was no change in lung function over time.</p> <p><i>Secondary outcome measure</i> Health status <i>Chronic Respiratory Disease Questionnaire 1 year compared to post-rehabilitation</i> There were differences between the groups ($F_{1,44}=6.28$, $p<0.016$) and there was a significant change over time ($F_{1,44}=6.75$, $p<0.002$) due to a steady decline in both groups. The exercise group had a mean (95% CI) decline of -8(-15 to -0.5) and the control group declined by a mean (95% CI) of -6(-11 to 0.6) from 8 weeks to 1 year.</p> <p>Chronic Respiratory Disease Questionnaire after 1 year compared to baseline <i>There was no significant difference between CRDO total score at baseline and that measured 1 year after rehabilitation</i></p>

	<p><i>between exercise and control groups. Health status improvements were therefore only maintained up to 6 months, but not up to 1 year.</i></p> <p><i>St. George's Respiratory Questionnaire 1 year compared to post-rehabilitation</i></p> <p>Showed no significant change over time ($F_{1,44}=1.273$, $p=0.265$) but significant variability between intervention groups ($F_{1,43}=4.24$, $p<0.05$). The exercise group improved by a mean (95% CI) of -2 (-7 to 3) points and the control group by a mean of -4 (-8 to 1) points.</p>
SIGN Quality Rating	++
Hierarchy of Evidence Grading	Ib
NCC CC ID	19371

Author / Title / Reference / Yr	van 't Hul, A., Kwakkel, G., Gosselink, R. (2002). The acute effects of non-invasive ventilatory support during exercise on exercise endurance and dyspnoea in patients with chronic obstructive pulmonary disease: A systematic review. Journal of Cardiopulmonary Rehabilitation, 22, 290-297.
N=	N=7 studies (N participants range from N=6 to N=39) Total N=96 participants Sites=Multiple
Research Design	Meta-analysis of RCT's (all crossover designs)
Aim	The aim of the study was to evaluate the effectiveness of different modes of NIVS during exercise to reduce exertional dyspnea and improve exercise endurance acutely, in patients with COPD.
Operational Definition	COPD as defined by the European Respiratory Society definition.
Population	Adult patients with COPD
Intervention	Non-invasive ventilatory support (N participants range from N=6 to N=39)
Comparison	Placebo (crossover studies- N= as above)
Outcome	<ul style="list-style-type: none"> • Exertional dyspnea • Effect of NIVS on exercise endurance • Effects of different modes of NIVS on exercise endurance, i.e. CPAP, PS and PAV
Characteristics	Mean age=64 years Severe airways obstruction with a mean forced expiratory volume in 1 second of 0.97 L. (35% predicted).
Results	<ul style="list-style-type: none"> • <u>Exertional dyspnea</u> <p>A statistically significant summary effect size was found for the outcome measure exertional dyspnea (0.57; CI 0.04-1.07:</p>

	<p>p=0.03). The overall heterogeneity statistic was not significant ($X^2=0.28$; p=NS). The average (weighted) improvement in Borg score for dyspnea during exercise with NIVS was 2 points (35% of control phase) below dyspnea scores during the control phase at isotime points.</p> <ul style="list-style-type: none"> • <u>Effect of NIVS on exercise endurance</u> In the best-case scenario of the effect of NIVS on exercise endurance, a statistically significant summary effect size was found (0.58; CI 0.29-0.87; p<0.001). The overall heterogeneity statistic was not significant ($X^2 =3.95$; p=NS). This summary effect size reflects a mean (weighted) improvement in exercise endurance of 3.3 minutes (55% of control phase). • <u>Effects of different modes of NIVS on exercise endurance, i.e. CPAP, PS and PAV</u> In the worst case scenario, the calculated summary effect size on exercise endurance was still statistically significant (0.33; CI 0.05-0.62; p=0.02), representing an average (weighted) increase in exercise endurance of 1.7 minutes (30% of control phase). The heterogeneity statistic was again not significant ($X^2 =2.3$; p=NS). <p>A significant homogeneous ($X^2=0.02$; p=NS) summary effect size was found only for PS (0.41; CI 0.06-0.77; p=0.03) representing an average (weighted) improvement in exercise endurance of 2.2 minutes (45% of control phase).</p>
SIGN Quality Rating	<p>++ This reflects the quality of the meta-analysis not the quality of the studies reviewed in the meta-analysis. The paper documents that the methodological quality score of the included papers varied from 31% to 54% of the maximum score of 13 points.</p>
Hierarchy of Evidence Grading	Ia
Included studies	O'Donnell et al (1988) N=6; Keilty et al (1994) N=8; Chrusch et al (1996) N=10; Dolmage et al (1997) N=10; Bianchi et al (1998) N=15; van't Hul et al (2001) N=39; Hernandez et al (2001) N=8
NCC CC ID	74

Section 7.13 Vaccination and anti-viral therapy

N=119 Literature search
N=89 Excluded from abstracts
N=30 Full papers ordered and of these:
N=4 Papers critically appraised
N=26 Papers excluded
N=4 paper found on NICE website
N=3 papers suggested by GDG (Nichols)

Influenza

Author	Publication Date	ID	SIGN Grade	Hierarchy
<p>NICE. Technology Appraisal Guidance No.15. Guidance on the use of Zanamivir (Relenza) in the treatment of influenza..</p> <p>Above documents (ID 1715) read in conjunction with NICE NHS HTA Zanamivir for the treatment of influenza in adults.</p>	<p>November 2000</p> <p>30.06.00 (Expiry date 01.01.01)</p>	1715	Replaced by TAG No. 58.	
<p>NICE. Technology Appraisal Guidance No.58. Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza.</p>	February 2003	1789	<p>Evidence Table</p> <p>Information supplemented with: Turner D, Wailoo A, Nicholson K et al. Systematic Review and Economic Decision Modelling for the Prevention and Treatment of Influenza A and B. NICE / Departments of Epidemiology and Public Health & Microbiology and Immunology, University of Leicester, and SchARR, University of Sheffield. April 2002 ID1786</p>	

NICE. Final Appraisal Document. Sanamivir, oseltamivir and amantadine for the treatment and prophylaxis of influenza	Document not dated		Awaiting publication re prophylaxis	
Tandon	1991	1618	-	1b
Poole (Cochrane)	2003 (Date of most recent amendment 02.01.02)	1523	+	1a
Nichols	1999	1724	+	11a
Pneumococcal				
Nichols	1999	216	+	11a
Leech	1987	1620	+	1b
Influenza and Pneumococcal				
Nichols	1999	1723	+	11a
Non specific immune stimulator				
Bonde	1986	1623	+	1b

Author / Title / Reference / Yr	Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza. Technology Appraisal Guidance No. 58. NICE. February 2003. Ref ID 1789 Systematic Review and Economic Decision Modelling for the Prevention and Treatment of Influenza A and B. Ref ID 1786
Research Design	Technology Appraisal Guidance
Operational Definition	Proportion of at risk COPD patients not defined.
Population	At risk adult population defined as including those who have chronic respiratory disease including COPD .
Characteristics	Characteristics of at risk COPD population not defined.

<p>Evidence Statements</p>	<p>All taken as direct quotes from the Technology Appraisal Guidance No. 58:</p> <p>Zanamivir</p> <p>The Assessment Report identifies five RCTs (un referenced in the TAG) of zanamivir in elderly people and otherwise at-risk people (% of COPD patients not defined). A meta analysis of these trials, N=371 people were treated with zanamivir and N=392 received placebo. On an ITT basis, the median time to alleviation of symptoms was 0.93 days sooner with zanamivir (95% CI -0.05 to 1.90 days). For people who had confirmed influenza within these groups (N=236 treated with zanamivir and N=248 placebo), the median time to symptom alleviation was 1.99 days sooner with zanamivir compared with placebo (95% CI; 0.90 to 3.08 days). The median times to return to normal activities were 0.09 days sooner for the treatment group (95% CI; -0.78 to 0.95 days) on an ITT basis and 0.20 day (95% CI; -0.79 to 1.19 days) for the influenza positive subgroup.</p> <p>There is some evidence that treatment with zanamivir for influenza reduces complications. An analysis of a set of trials including both otherwise healthy and at risk individuals (proportion of COPD not defined) found that in a pooled subgroup of 230 high risk adults and children with laboratory confirmed influenza, antibiotics were required by 24% in the placebo group and 13% in the zanamivir group; odds ratio 0.49, 95% CI; 0.23 to 1.04.</p> <p>In clinical trials, Zanamivir has not been extensively tested in people with chronic respiratory disease. In post licensing experience, there have been very rare reports of allergic reactions such as facial and oropharyngeal oedema, rash and urticaria.</p> <p>Oseltamivir</p> <p>The Assessment Report identifies five RCTs of oseltamivir in elderly people and otherwise at-risk adults (proportion of COPD not defined) that have been used in a meta analysis. The analysis involved 557 people treated with oseltamivir and 577 with placebo. On an ITT basis, the median time to alleviation of symptoms was 0.35 days sooner with oseltamivir (95% CI; -0.71 to 1.40 days). For people who had confirmed influenza within these groups (341 treated with oseltamivir and 387 who received placebo), the median time to symptom alleviation was 0.45 days sooner with oseltamivir compared with placebo (95% CI; -0.97 to 1.88 days). With oseltamivir, the median times to return to normal activities were 2.45 days sooner for the treatment group (95% CI; 0.05 to 4.86) on an ITT basis and 3.00 days (95% CI; 0.13 to 5.88 days) for the influenza positive subgroup.</p> <p>There is some evidence that treatment with oseltamivir treatment for influenza reduces complications. In an overlapping set of trails involving both otherwise health and at risk people (proportion of COPD not defined) who were diagnosed as influenza positive, 19 out of 1063 receiving placebo developed pneumonia, compared with 9 out of 1350 receiving oseltamivir (odds ratio 0.37, CI 0.15 to 0.86).</p> <p>Oseltamivir, in clinical trials, is generally well tolerated, but has been associated with a higher rate of nausea (3 to 7% higher) and vomiting (2% higher) compared with placebo.</p>
<p>Recommendations</p>	<p>All taken as direct quotes from the Technology Appraisal Guidance No. 58:</p> <p>“Within licensed indications, zanamivir and oseltamivir are recommended for the treatment of at-risk adults who present with influenza like illness (ILI) and who can start therapy within 48 hours of the onset of symptoms.</p> <p>Anti-influenza drugs appear to act independently of vaccination and provide additional barriers to the influenza virus where the vaccine does not work.</p>

	<p>Zanamivir Zanamivir is a neuraminidase inhibitor and is taken using an inhaler (Diskhaler). It is licensed for the treatment of influenza A and B. Zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir they should be made aware of the risks and have a fast-acting bronchodilator available.</p> <p>Oseltamivir Oseltamivir is a neuraminidase inhibitor. It can be taken orally and is licensed for the treatment of influenza A and B.”</p>
Hierarchy of Evidence Grading	NICE Technology Appraisal Guidance
Papers included	Not specified
NCC CC ID	1789

Author / Title / Reference / Yr	Tandon, M. K. & GebSKI, V. 1991, "A controlled trial of a killed Haemophilus influenzae vaccine for prevention of acute exacerbations of chronic bronchitis", <i>Australian & New Zealand Journal of Medicine</i> , vol. 21, pp. 427-432. Ref ID: 1618
N=	N=64 participants. Location=Western Australia Sites=1 site. Duration=6/12 follow up
Research Design	Double blind RCT
Aim	To find out whether oral immunisation of patients, with documented chronic bronchitis and recurrent respiratory tract infections, using a killed H. influenzae vaccine vs placebo, would reduce the frequency of infective episodes of bronchitis, reduce the need for antibiotics, reduce the carriage rate of the putative pathogen.
Operational Definition	Chronic bronchitis (MRC criteria) and at least two acute infective episodes per year for more than 3 years. Severe chronic obstructive airways disease as defined by FEV1<1L & at least two acute infective episodes More than 3 isolations of H. influenza on microbiological examination of sputum in the past 2 years & history of recurrent respiratory tract infection.
Population	Patients with chronic bronchitis (See comments section*)
Intervention	N=31 Formalin-killed non-serotypable biotype-1 H.influenzae (oral vaccine)
Comparison	N=33 Placebo (lactose) (oral)
Outcome	Number of reported infections Number of patients developing infections Number of courses of antibiotics Number of patients who received antibiotics Carriage rate of H.Influenzae

Characteristics	Mean age ratio male/female=22:9/30:3 Mean FEV1 active/placebo=0.96/0.89 Mean VC active/placebo=1.82/2.00 No p-values given. Smoking history- unclear whether units are packets of individual cigarettes or individual cigarettes- no time frame specified.
Results	Difference in number of reported infections between the treatment and placebo group is non-significant (p=0.116). Difference in number of infections between the treatment and placebo group is significantly less in treatment group (p=0.024, 95% CI, 1.114-4.625; relative risk 2.27). Difference in number of courses of antibiotics given between the treatment and placebo group was significant (p=0.042; no CI given). Difference in number of patients who received antibiotics in the treatment group vs placebo group was non-significant (p=0.242). Non-significant reduction in carriage rate of H.Influenzae (p=0.418).
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1618

Author / Title / Reference / Yr	Poole PJ, Chacko E, Wood-Baker RWB, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease.(Cochrane Review). <i>The Cochrane Library.Oxford:Update Software 2003;Issue 3</i> . Date of most recent amendment: 2 January 2002
N=	N=9 RCTs but only 4 RCT's are meta-analysed as only 4 trials studied COPD alone (Gorse, 1997; Fell, 1977; Howells, 1961; MRC, 1980). N=varied from 29-55 participants. Total sample size N=215 Location=St. Louis, Oxfordshire, NW Wolverhampton, No details for one site Duration=(varied from 3 weeks (MRC 1980) to 3-4 months (Howells 1961).
Research Design	Cochrane Systematic Review
Aim	To determine whether influenza vaccination: 1. Reduces respiratory illness in people with COPD. 2. Reduces mortality in people with COPD. 3. Is associated with excess adverse events in people with COPD.
Operational Definition	COPD as defined by the American Thoracic Society & the European Respiratory Society
Population	N=215. Adults with stable COPD
Intervention	More than one annual influenza vaccination of the following types: - live attenuated whole virus

	- inactivated or split-virus type vaccine These may be administered by either intramuscular or intranasal routes.
Comparison	Placebo
Outcome	<ol style="list-style-type: none"> 1. Number of acute exacerbations of COPD (defined as an increase in breathlessness and/or the volume and/or purulence of sputum). 2. Number of days of disability from respiratory illness (days in bed/days of work/days unable to undertake normal activity) 3. Number of hospital admissions 4. Mortality in the year following vaccination. 5. Change in lung function from baseline at the end of study period. 6. Adverse effects of treatment.
Characteristics	<p>Age=57.9 based on the 3 trials that reported mean age / Gender=ranged from 64% male to 100% male.</p> <p>Severity of COPD= unclear in Fell (1977).</p> <p>Severity of COPD= severe (FEV1/FVC%<70%) in Gorse (1997).</p> <p>Severity of COPD= FEV1>1L in MRC 1980.</p> <p>Howells (1961) graded severity according to a graded system (grade I – gradeIII)</p>
Results	<p>Influenza vaccination versus placebo</p> <p>Exacerbations</p> <p>Two studies (Howells 1961 and Fell 1977) produced opposite results. Howells (using inactivated vaccine) in favour of vaccination and Fells (using live attenuated virus) in favour of the control group. As a result the meta analysis showed no overall difference between vaccinated and placebo treated participants for the number of patients having an exacerbation.</p> <p>Authors state, “The data on exacerbations reflect primarily the findings of Howells 1961. That was a careful study, of high methodological quality, carried out using inactivated vaccine in 55 patients. This study demonstrated a reduction of 0.45 exacerbations per patient over the study period. This reduction was due mainly to a reduction in the number of late exacerbations in the vaccinees. No increase in early exacerbations was seen. Vaccine effectiveness (expressed as 1-(rate vaccine group/rate control group)) in this study was 44% for all exacerbations and 91% for late exacerbations. The authors of the study concluded that protection did not develop until at least three weeks after immunisation. The other RCT in COPD patients that assessed the number of patients who had exacerbations (Fell 1977), found that influenza vaccination was not effective and that upper respiratory tract symptoms were reported more frequently by vaccinees than placebo recipients in the first 2 weeks after immunisation. This study used live attenuated virus whereas Howells had used inactivated virus. It was of lower quality than the Howells study, and it was unclear how well the groups were matched at baseline. The author commented that this study was performed in a non-epidemic year, although there is no information in either Fell 1977 or Howells 1961 regarding the match between vaccine and influenza strains”.</p> <p>“In one study (Howells 1961) of inactivated vaccine in COPD patients there was a significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo (weighted mean difference (WMD) -0.45, 95% confidence interval -0.75 to -0.15, p = 0.004). This difference was mainly due to the reduction in exacerbations occurring after 3 weeks (WMD -0.44, (95% CI -0.68 to -0.20, p<0.001). The number of patients experiencing late exacerbations was also significantly</p>

	<p>less (OR= 0.13, 95%CI 0.04 to 0.45, p=0.002)".</p> <p>Hospitalisation, mortality rates and lung function</p> <p>Effects of vaccination on hospitalisations, mortality rates or lung function rates were seldom reported in trials. Those trials reporting these outcomes found no effect on hospitalisation (Howells 1961), mortality (Howells 1961), and lung function rates (MRC 1980).</p> <p>Adverse Events</p> <p>Cochrane authors state: "Adverse effects were seldom reported in the trials in COPD patients. Only Fell 1977 reported early (within 2 weeks of vaccination) upper respiratory tract symptoms. There was no difference between vaccinated and control patients in terms of breathlessness and tightness (OR=1.28, 95%CI 0.38-4.31, p=0.696), cough (OR=4.09, 95%CI 0.74-22.49, p=0.106), or sputum production (OR=2.03, 95%CI 0.48-8.66, p=0.338). The occurrence of wheeze within the first 2 weeks was greater in vaccinated patients (OR=3.57, 95%CI 1.10-11.56, p=0.034). Breathlessness was recorded significantly less often (p<0.05) in the 5 of 21 patients who had a serological response to vaccination than in the placebo group".</p> <p>However, the primary paper for the Fell study states: "During the surveillance period, the number of weeks in which the scores for symptoms of breathlessness, tightness, wheeze, and cough were in excess of baseline were significantly greater for all symptoms (p<0.05) in the vaccinated group (15/20) than in the placebo group (7/22)". (Un referenced / un validated symptom severity score).</p> <p>Live attenuated, intranasal plus inactivated versus placebo intranasal plus inactivated group</p> <p>In terms of assessing the add on benefit of live intranasal virus (Gorse 1997), no significant difference was found between treatment and placebo group in exacerbations, lung function or adverse effects.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ia
Papers specific to COPD population	Fell (1977) N=45; Gorse (1997) N=29; Howells (1961) N=55; MRC (1980) N=86;
NCC CC ID	1523

Author / Title / Reference / Yr	Leech, J. A., Gervais, A., & Ruben, F. L. 1987, "Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease", <i>Canadian Medical Association Journal</i> , vol. 136, no. 4, pp. 361-365. Ref ID: 1620
N=	N= 189 (N=92 experimental group) (N=97 control group). Location=(Montreal) Sites=(1 site). Data collected 1981. Duration=(2 years- 6 monthly interval follow-ups)
Research Design	Double blind RCT
Aim	To demonstrate a protective role of polyvalent pneumococcal vaccine in severe COPD.
Operational Definition	No operational definition of COPD reported. Clinical diagnosis of COPD and an FEV1 <1.5L

	<p>Definitions given for:</p> <p>Upper respiratory tract infection: presence of runny nose; fever; increased cough without an increase in the quantity or a change in the colour of the sputum.</p> <p>Lower respiratory tract infection: a combination of fever, increased cough and a change in the colour or an increase in the sputum quantity.</p> <p>Pneumonia: Presence of symptoms of a lower respiratory tract infection and evidence of a new infiltrate on a chest roentogram.</p>
Population	<p>Stable, ambulatory population attending chest clinic with "severe COPD": COPD diagnosis (including chronic bronchitis and emphysema but not asthma, cystic fibrosis or bronchiectasis) FEV1 < 1.5L Previous pneumococcal vaccine excluded</p>
Intervention	N=92 Influenza vaccine & 14-valent pneumococcal polysaccharide vaccine by injection
Comparison	N=97 Influenza vaccine & saline placebo by injection
Outcome	Death rate / Hospital admissions / Emergency visits / Mean length of hospital stay
Characteristics	<p>Mean age control group/ experimental group=69/66yrs. Age range 40 to 89 years. Men control group/experimental group=69/66 FEV1/FVC in control group=0.96/2.13 L FEV1/FVC in experimental group=0.94/2.18 L</p>
Results	Over a two-year period, the rates of death, hospital admissions and emergency visits and the mean length of hospital stay were not significantly different in the two groups.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1620

Author / Title / Reference / Yr	Bonde, J., Dahl, R., & Edelstein, R. 1986, "The effect of RU 41.740, an immune modulating compound, in the prevention of acute exacerbations in patients with chronic bronchitis", <i>European Journal of Respiratory Diseases</i> , vol. 69, no. 4, pp. 235-241. Ref ID: 1623
N=	N=198 participants. Location- France Sites- 4 sites. Duration=(6 month follow up)
Research Design	Multicentre, double blind, randomised parallel 3 group placebo controlled trial.
Aim	To examine the effect of Biostim (RU 41.740) a new non-specific immune modulator in reducing number of acute exacerbations in patients with chronic bronchitis.

Operational Definition	Chronic bronchitis stages 2 & 3 (MRC criteria) An acute exacerbation was defined as: increased purulence, viscosity or volume of sputum associated with one or more of the following: temperature above 38C, worsening cough, increased dyspnea and/or increased difficulty in expectorating.
Population	Patients with chronic bronchitis stages 2 and 3 (MRC criteria); > 18 yrs; experienced >3 exacerbations during the year prior to the study. Exclusion criteria are available.
Intervention	Bioestim 2mg/day (=group B) - tablets Bioestim 8mg/day (=group C) - tablets Administered for 7 consecutive days on alternate weeks for 3 successive months during the winter.
Comparison	Placebo (=group A) - tablets
Outcome	Number of exacerbations / Duration of exacerbations / Duration of antibiotic therapy. Measured at 3 and 6 months.
Characteristics	Age range=26-78/mean=60.5yrs Male/female ratio=125/69 Smokers N=145/ex-smokers N=41/Non-smokers N=8 FEV1=48.5%; FEV1/VC= 28.5%
Results	<p>3 month evaluation</p> <p>Number of exacerbations Significantly lower number of exacerbations in group B (=Bioestim 2mg/day) (p=0.005; CI not stated).</p> <p>Subgroup analysis: <i>Stage of chronic bronchitis:</i> Linear modelling on the number of exacerbations allowing for stage of chronic bronchitis highlighted that there was a significant stage / treatment interaction (p=0.03). The analysis was undertaken separately for stage 2 and stage 3 patients. Stage 2 demonstrated no significant treatment effect. Stage 3 subgroup demonstrated a highly significant treatment effect (p=0.0002).</p> <p><i>FEV1</i> Pre treatment FEV1 was significantly related to stage (p=0.005) and since it is a more quantifiable parameter, the analysis was repeated substituting FEV1 for stage. Among subjects with a decrease in FEV1 exceeding 60% predicted, those in the 2mg group had significantly fewer infections (p=0.02). In the group with an FEV1 <60% decrease of predicted, there was no significant treatment effect.</p> <p>Duration of exacerbations No significant reduction in the duration of the infections was obtained in the treatment period (11.4 days in group A/8.7 days in group B/9.5 days in group C).</p> <p>Duration of antibiotic therapy No significant reduction in antibiotic consumption or carry over effect could be demonstrated.</p> <p>6 month evaluation No differences were observed between the groups for number of exacerbations. duration of exacerbations or consumption of</p>

	antibiotics. Side effects No serious side effects occurred. No differences between the three groups detected for side effects.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1623

Author / Title / Reference / Yr	Nichol, K. L. 1999, "The additive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease", <i>Vaccine</i> , vol. 17 Suppl 1, p. S91-S93. Ref ID: 1723
N=	Total N=1898 participants Location= Large managed care organisation in the Minneapolis-St. Paul, MN (USA) Sites=21 clinics
Research Design	Retrospective cohort study based on data from the surveillance of influenza from the Minnesota Department of Health.
Aim	To assess the benefits of both influenza and pneumococcal vaccinations among elderly persons.
Operational Definition	Data obtained from the administrative data bases of the health care organisation was used to compare the risk of hospitalisation and death, during 3 influenza seasons, among vaccinated and unvaccinated elderly persons with chronic lung disease, while controlling for covariates and confounders.
Population	Elderly patients with a diagnoses of chronic lung disease.
Intervention	Influenza vaccination alone; Pneumococcal vaccination alone; Both influenza & pneumococcal vaccination
Comparison	N/A
Outcome	Hospitalisations rates for pneumonia and influenza Death rates Over each of 3 influenza seasons: 1993-1994 1994-1995 1995-1996
Characteristics	Mean age= 69.92yrs Male = 48.8% History of pneumonia = 17.6%
Results	Influenza vaccination rates:

	<p>72% (1993-1994) 74% (1994-1995) 75% (1995-1996) Influenza & pneumococcal vaccination rates: 44% (1993-1994) Pneumococcal vaccination rates: 23% outcome period Influenza vaccination alone: Reduction in the risk for hospitalisation for pneumonia- 52% (95% CI, 18-72) Reduction in the risk of disease- 70% (95% CI, 57-89) Pneumococcal vaccination alone: Reduction in the risk for hospitalisation for pneumonia not statistically significant- 27% (95% CI -13-52) Reduction in the risk of disease- 34% (95% CI, 6-54) Both influenza & pneumococcal vaccination: Reduction in the risk for hospitalisation for pneumonia- 63% (95% CI, 29-80) Reduction in the risk of deaths 81% (95% CI, 68-88). No evidence of an interaction between the vaccinations (p>0.5). Benefits are additive.</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	IIa
NCC CC ID	1723

Author / Title / Reference / Yr	Nichol, K. L., Baken, L., & Nelson, A. 1999, "Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease", <i>Ann Intern Med</i> , vol. 130, no. 5, pp. 397-403. Ref ID: 1724
N=	Total N= 1898 participants Location= Data obtained from the administrative databases of Group Health, Minneapolis-St Paul, MN (USA) Sites=21 clinics
Research Design	Retrospective multiseason cohort study based on data obtained from the administrative databases of Group Health
Aim	To define the effects of influenza and the benefits of influenza vaccination in elderly persons with chronic lung disease.
Operational Definition	Data obtained from the administrative data bases of the health care organisation was used to compare outcomes in vaccinated and unvaccinated elderly persons with chronic lung disease for 3 influenza seasons after adjustment for baseline demographics and health

	characteristics.
Population	All Group Health members who were > 65 yrs, received a diagnosis of chronic lung disease (ICD-9-CM) during the previous 12 months, and were alive on the first day of the outcome period.
Intervention	Vaccinated participants N=1366
Comparison	Unvaccinated participants N=532
Outcome	Outcomes for the 1993-1994, 1994-1995, 1995-1996 influenza seasons. Primary outcomes Number of hospitalisations for pneumonia and influenza. Number of hospitalisations for all acute and chronic respiratory conditions and deaths from all causes. Secondary outcome Outpatient visits for pneumonia and influenza. Outpatient visits for all acute and chronic conditions.
Characteristics	Mean age vaccinated/unvaccinated participants- 73.5/75.0 years Male gender vaccinated/unvaccinated participants- 51.2%/42.7% History of pneumonia vaccinated/unvaccinated participants- 16.5%/20.3% Pneumococcal vaccination vaccinated/unvaccinated participants- 49.6%/31.2%
Results	Vaccination rates: 1993-1994 (72%), 1994-1995 (74%), 1995-1996 (75%). Among participants who had been vaccinated before the third influenza season, 76% had received immunisations for the two previous seasons and 21% had received one immunisation over the two previous seasons. Primary outcomes Number of hospitalisations for pneumonia and influenza- N=112. Number of hospitalisations for all acute and chronic respiratory conditions and deaths from all causes- N=566. Secondary outcome Outpatient visits for pneumonia and influenza- N=1113. Outpatient visits for all acute and chronic conditions- N=9517. Deaths- N=149. Participants disenrolled- N=259. Unvaccinated participants Overall annualised incidence for pneumonia and influenza was 55 hospitalisations per 1000 person-years (95% CI, 34-76 per 1000). This doubled to 111 hospitalisations per 1000 person-years) during the influenza seasons (p<0.001). Vaccinated participants Annualised hospitalisation rates were 41 per 1000 person-years (CI, 30-51 per 1000 person-years) during the interim periods and 45 per 1000 person-years (CI, 33-56 per 1000 person-years) during the influenza seasons (p=0.11). Reduction in the number of hospitalisations for pneumonia and influenza= 52% (adjusted risk ratio, 0.48; p=0.008).

	<p>Reduction in risk for death= 70% (adjusted odds ratio, 0.30; p<0.001).</p> <p>Number of hospitalisations for all respiratory conditions did not differ significantly between the two groups (RR, 0.76; p=0.13).</p> <p>For outpatient visits, influenza vaccination was not associated with a lower risk for having at least one visit for either pneumonia (OR, 0.95; p>0.2) or all respiratory conditions (OR, 0.95; p>0.2) during the influenza season.</p> <p>Among persons who had at least one visit, the numbers of outpatient visits were lower for both pneumonia and influenza (RR, 0.64; p=0.002) and all respiratory conditions (RR, 0.89; p=0.002).</p> <p>The rates of hospitalisation for the two control outcomes were similar in the two study groups (for hospitalisations for pneumonia and influenza during the interim periods: RR, 0.93 [CI, 0.52-11.65]; p>0.2; for hospitalisations for noncardiopulmonary conditions during the influenza season: RR, 0.96 [CI, 0.70-1.31]; p>0.2).</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	IIa
NCC CC ID	1724

Author / Title / Reference / Yr	Nichol, K. L., Baken, L., Wuorenma, J., & Nelson, A. 1999, "The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease", <i>Archives of Internal Medicine</i> , vol. 159, no. 20, pp. 2437-2442. Ref ID: 216
N=	Total N=1898 participants Location= Staff-model health maintenance organisation (covering 21 clinics) -Minneapolis-St Paul. Sites=21 clinics
Research Design	Retrospective cohort study- based on the Staff-model health maintenance organisation database (covering 21 clinics).
Aim	To assess the association of pneumococcal vaccination with hospitalisations for pneumonia, influenza, and death.
Operational Definition	Using administrative data, hospitalisations for pneumonia & influenza, and death were compared for vaccinated and unvaccinated subjects using multivariate models to control for subjects baseline demographic and health characteristics.
Population	All members of the staff-model health maintenance organisation who were: >65 yrs A diagnosis of chronic lung disease (ICD-9-CM) During the preceding 12 months (01/10/1992-30/09/1993) Who were alive on the first day of the outcome period Who were continuously enrolled throughout the 12-month baseline period
Intervention	Vaccinated participants N=1280 (vaccinated before 11/15/93 N=843; vaccinated after 11/15/93).
Comparison	Not vaccinated participants

	N=618
Outcome	Association of pneumococcal vaccination with: Hospitalisations for pneumonia Influenza Death from all causes The additive benefits of combined influenza and pneumococcal vaccination
Characteristics	Two influenza seasons were taken into account. The first influenza season was taken from 15.11.93 through to 30.03.94 and second influenza season was 15.11.94 through to 30.03.95. Baseline characteristics of the study participants according to pneumococcal vaccination status was presented in the following format only: Mean Age yrs Vaccinated before 15.11.93 / vaccinated after 15.11.93 / not vaccinated=73.6yrs/74.1yrs/74.9yrs Male % Vaccinated before 15.11.93 / vaccinated after 15.11.93 / not vaccinated=50.5/49.9/45.6 History of pneumonia % Vaccinated before 15.11.93 / vaccinated after 15.11.93 / not vaccinated=17.3/14.2/20.4 Influenza vaccination % Vaccinated before 15.11.93 / vaccinated after 15.11.93 / not vaccinated=80.3/78.5/56.0
Results	Pneumococcal vaccination was associated with A 43% reduction (adjusted risk ratio [RR], 0.57; 0.57; p=0.005) in the number of hospitalisations for pneumonia and influenza. A 29% reduction (adjusted RR, 0.71; p=0.008) in the risk for death from all causes. For the control outcome of nonpneumonia hospitalisations, the rates did not differ significantly between the 2 groups (adjusted RR, 0.91; 95% CI, 0.77-1.07; p=0.24). During the 2 influenza seasons included in the study, the effects of influenza vaccination were additive to those of pneumococcal vaccination. Among persons who had received both vaccinations, there was a 72% reduction (adjusted RR, 0.28; 95% CI, 0.14-0.58; p<0.001) in the number of hospitalisations for pneumonia and influenza and an 82% reduction (adjusted odds ratio [OR] 0.18; 95% CI, 0.11-0.31; p<0.001) in the risk of death when compared with those who had received neither vaccination. There was no evidence for interaction between the 2 vaccinations (influenza and pneumococcal vaccinations) for either outcome (p=0.96 and p=0.59, respectively).
SIGN Quality Rating	+
Hierarchy of Evidence Grading	IIa
NCC CC ID	216

Section 7.15 Alpha-1 antitrypsin replacement therapy

N=93 Literature search
N=77 Excluded from abstracts
N=16 Full papers ordered and of these;
N=3 critically appraised
N=13 papers excluded

Author	Publication Date	ID	SIGN Grade	Hierarchy
Dirksen, A., Dijkman, J. H., Madsen, F., Stoel, B., Hutchison, D. C. S., Ulrik, C. S., Skovgaard, L. T., Kok-Jensen, A., Rudolphus, A., Seersholm, N., Vrooman, H. A., Reiber, J. H. C., Hansen, N. C., Heckscher, T., Viskum, K., & Stolk, J. 1999, "A randomized clinical trial of alpha1-antitrypsin augmentation therapy", <i>American Journal of Respiratory & Critical Care Medicine</i> , vol. 160, no. 5 I, pp. 1468-1472. Ref ID: 1249	1999	1249	+	1b
The Alpha 1-Antitrypsin Deficiency Registry Study Group 1998, "Survival and FEV1 decline in individuals with severe deficiency of alpha 1-antitrypsin. ", <i>American Journal of Respiratory & Critical Care Medicine</i> , vol. 158, pp. 49-59. Ref ID: 1336 McElvaney, N., Stroller, J., & Buist, S. 1997, "Baseline Characteristics of Enrollees in the National Heart, Lung and Blood Institute Registry of □1-Antitrypsin Deficiency.", <i>Chest</i> , vol. 111, pp. 394-403.	1998	1336 / 1354 / 1355	+	111

Ref ID: 1354				
Alpha 1-Antitrypsin Deficiency Registry Study Group, Schluchter, M., Barker, A. F., Crystal, R. G., Robbins, R. A., Stocks, J. M., STOLLER, J., & Wu, M. C. 1994, "A registry of patients with severe deficiency of alpha 1-antitrypsin: design and methods.", <i>Chest.</i> , vol. 106, pp. 1223-1232. Ref ID: 1355				
Seersholm, N., Wencker, M., Banik, N., Viskum, K., Dirksen, A., Kok, J. A., & Konietzko, N. 1997, "Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. [see comments]", <i>European Respiratory Journal</i> , vol. 10, pp. 2260-2263. Ref ID: 1258	1997	1258	-	11b

Author / Title / Reference / Yr	Dirksen, A., Dijkman, J. H., Madsen, F., Stoel, B., Hutchison, D. C. S., Ulrik, C. S., Skovgaard, L. T., Kok-Jensen, A., Rudolphus, A., Seersholm, N., Vrooman, H. A., Reiber, J. H. C., Hansen, N. C., Heckscher, T., Viskum, K., & Stolk, J. 1999, "A randomized clinical trial of alpha1-antitrypsin augmentation therapy", <i>American Journal of Respiratory & Critical Care Medicine</i> , vol. 160, no. 5 I, pp. 1468-1472. Ref ID: 1249
N=	N=56 Duration & location=1991 to 1995 Danish population / 1993 to 1997 Dutch population.
Research Design	Randomised, parallel, double-blind, placebo controlled trial
Aim	To investigate whether α 1-antitrypsin replacement therapy prevents the progression of pulmonary emphysema in patients with α 1-antitrypsin deficiency.
Operational Definition	α 1-antitrypsin deficiency of PI*ZZ phenotype (FEV1 between 30% and 80% of predicted)

Population	N=26 Danish / N=30 Dutch Moderate emphysema / Ex smokers (validated by 1/12 urinary cotinine throughout trial) Participants were stratified by age, FEV1 and nationality Danish population active / placebo N=13/13. Cutch population active / placebo N=15/15
Intervention	α 1-antitrypsin 250mg/kg infusions at 4 wk intervals for at least 3 yrs
Comparison	Albumin 625 mg/kg infusions at 4 wk intervals for at least 3 yrs
Outcomes	Respiratory laboratory testing at baseline and every 3/12, 15 mins after nebulised Terbutaline 5mg, VC, FVC & FEV1 Self administered spirometry performed morning and evening at home Yearly lung density computed tomography (CT) to assess the degree of emphysema
Characteristics	Male/female ratio differed between centres (Danish 14/12 whilst Dutch 20/10) Mean age – Danish 50yrs / Dutch 45yrs FEV1 – Danish 1,570 ml, 49% predicted / Dutch 1,660 ml, 47% predicted.
Results	Primary outcome: FEV1 There were no significant differences between the α 1-antitrypsin and comparison group for daily self-administered FEV1. α 1-antitrypsin group showed an annual decline of 26.5 +/- 15.1 ml compared to the control group of 25.2 +/- +/- 22.0 ml, p=0.96 Secondary outcome: Lung density Loss of lung tissue measured by CT was 2.57 +/- 0.41 g/L/yr for placebo compared with 1.5 +/- 0.41 g/L/yr for α 1-antitrypsin, equating to an annual loss of lung tissue by 1.07 g/L in comparison to the placebo group (p=0.07). The study authors state, “Power analysis showed that this protective effect would be significant in a similar trial with 130 pts” and that “lung density measurements by CT may facilitate future RCTs”. There were no significant differences in the baseline and the time trend lung function variables for either group. No adverse outcomes were observed in either group.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1249

Author / Title / Reference / Yr	<p>The Alpha 1-Antitrypsin Deficiency Registry Study Group 1998, "Survival and FEV1 decline in individuals with severe deficiency of alpha 1-antitrypsin. ", <i>American Journal of Respiratory & Critical Care Medicine</i>, vol. 158, pp. 49-59. Ref ID: 1336</p> <p>McElvaney, N., Stoller, J., & Buist, S. 1997, "Baseline Characteristics of Enrollees in the National Heart, Lung and Blood Institute Registry of α1-Antitrypsin Deficiency.", <i>Chest</i>, vol. 111, pp. 394-403. Ref ID: 1354</p> <p>Alpha 1-Antitrypsin Deficiency Registry Study Group, Schluchter, M., Barker, A. F., Crystal, R. G., Robbins, R. A., Stocks, J. M., Stoller, J., & Wu, M. C. 1994, "A registry of patients with severe deficiency of alpha 1-antitrypsin: design and methods.", <i>Chest</i>, vol. 106, pp. 1223-1232. Ref ID: 1355</p>
N=	N=1,129. Location=37 clinical centres. Geographic site=USA & Canada. Duration=From March 1989 through October 1992. Follow up over a 44-month period, continued through to April 1996.
Research Design	Prospective, longitudinal natural history study. Cohort Design (Exposed vs non exposed to augmentation therapy)
Aim	The National Heart, Lung and Blood Institute and the National Institutes of Health initiated a registry of people with of α 1-antitrypsin deficiency in order to define the natural history and clinical course of the disorder.
Operational Definition	Serum α 1-antitrypsin levels $\geq 11\mu\text{mol/L}$ confirmed by a Central Phenotyping Laboratory OR A ZZ or ZNull genotype identified by genomic DNA analysis.
Population	Patients with Severe Deficiency of Alpha-1-Antitrypsin
Augmentation Therapy	<p>Classification Patients were classified as always, partly, or never receiving α1-Antitrypsin therapy. Classification of these subjective categories is provided.</p> <p>Augmentation Therapy Use Among the 1,129 participants enrolled in the study, 34% of patients never received augmentation therapy, 35% always received therapy and 32% were partly receiving therapy. 20% patients were receiving α1-Antitrypsin therapy at enrolment in the Registry Within 3 months of enrolling, this percentage increased to 46%. 58% of patients receiving therapy were those with FEV1 $<30\%$ predicted. 54% of patients with FEV1 between 30% and 49% predicted were also receiving augmentation therapy within 3/12 of enrolment.</p> <p>Infusion Regimes 53% of patients received augmentation therapy once weekly by infusion 23% received therapy by monthly infusions 24% received intravenous therapy every 2 or 3 weeks</p>

Outcomes	Followed for 3.5 to 7 years with spirometry measurements every 6 to 12 months.
Characteristics	Average age 46 +/- 10 years / 72% symptomatic / 99% white / 56% male / 20% never-smokers, 72% ex smokers and 8% current smokers / 79% family history of lung disease / 25% family history of liver disease
Results	<p>Mortality 5-year mortality was 19% (95% CI: 16 to 21%) Age and baseline FEV1 % predicted were significant predictors of mortality (N=1,048, multivariate analyses >6 months after enrolling). Patients receiving augmentation therapy had decreased mortality (RR 0.64, 95% CI: 0.43 to 0.94, p=0.02) compared to those not receiving therapy. In those participants with initial FEV1 <50% predicted, mortality was significantly higher (p<0.001) for patients who never as opposed to sometimes or always received augmentation therapy. Use of augmentation therapy was associated with lower mortality in the subgroup with initial FEV1 values of 35 to 49% predicted (ATS Stage II) (RR 0.21, 95% CI 0.09 to 0.50, p<0.001)</p> <p>FEV1 Mean FEV1 decline was 54ml/yr with more rapid decline in males, aged 30 to 40 yrs, current smokers, FEV1 35 to 79% predicted and those who ever had a bronchodilator response. (N=927 patients with two+ FEV1 measurements >1 yr apart). Among all patients, there was no significant difference in FEV1 decline between augmentation therapy groups. Among patients with a mean FEV1 35 to 49% predicted, FEV1 decline was significantly slower for patients receiving augmentation therapy compared to those who were not (mean difference 27ml/yr, 95% CI: 3 to 51 ml/yr, p=0.03).</p>
SIGN Quality Rating	+
Hierarchy of Evidence Grading	11b
NCC CC ID	1336 / 1354 / 1355

Author / Title / Reference / Yr	Seersholm, N., Wencker, M., Banik, N., Viskum, K., Dirksen, A., Kok, J. A., & Konietzko, N. 1997, "Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. [see comments]", <i>European Respiratory Journal</i> , vol. 10, pp. 2260-2263. Ref ID: 1258
N=	N=295 Location=two geographical populations. Geographic site= Danish and German.
Research Design	Cohort study.
Aim	To compare the decline in FEV1 between Danish patients who had never received augmentation therapy and German patients

	treated with weekly infusion of α 1- antitrypsin.
Operational Definition	Not provided
Population	N=97 Danish people with α 1- antitrypsin deficiency N=198 German people with α 1- antitrypsin deficiency
Intervention	German patients with α 1- antitrypsin deficiency and weekly infusions of α 1- antitrypsin 60-mg/kg. Duration not stated.
Comparison	Danish patients with α 1- antitrypsin deficiency and no augmentation therapy
Outcomes	Decline in FEV1 German population: Lung function measures were carried out prior to commencing augmentation therapy, 1 wk after the start of the study, 3 and 6 months post commencement and then 6 monthly for the treated group. Danish population: Two-spirometry measurements at least 1 yr apart.
Characteristics	German population (treated): PiZZ phenotype / ex smokers / received augmentation therapy for at least 1 year / spirometry was performed by specially trained staff as per European recommendations / FEV1 <65% pred / post bronchodilator FEV1. Initial FEV1 % predicted was significantly lower at baseline in the treated group compared with the Danish untreated population (FEV1 % pred 37 vs 42 respectively). There were also significantly more males in the German treated population at baseline compared to the untreated group (72 vs 57% respectively). There average follow up time was 3 yrs in the German group and 6 yrs in the Danish group. Average age at entry 46 yrs. Danish population (untreated): α 1-antitrypsin Pi type was determined by in some cases (numbers not provided) by laboratory phenotyping, however, where this had not been performed the patients were “assumed to have phenotype PiZZ or PiZ0 if α 1 antitrypsin serum level was less than 12 μ mol/L”. Spirometry was performed by referring physician or chest clinic according to European recommendations. Not stated whether post bronchodilator FEV1 measured. FEV1 % pred at inclusion not documented. Ex smokers. See above for demographic differences between the two groups. Average age 45 yrs at entry.
Results	FEV1 There was a significant difference between the two groups of 22ml/yr (p=0.02). Treated group – Annual declines of 53ml/yr (95% CI, 48 to 58 ml/yr) Untreated group – Annual declines of 75 ml/yr (95% CI, 63 to 87 ml/yr) To explore whether the FEV1 differences between the two groups were due to the initial baseline differences between the groups, the impact of variables such as gender, follow up time and initial FEV1% were analysed. Neither gender nor follow up time had any influence on FEV1. Stratification by initial FEV1 % predicted showed a significant effect of the treatment in the group of α 1 antitrypsin deficient patients in the augmentation treated only in the group of patients with an initial FEV1% pred of 31 to 65%. In this group FEV1 was reduced by 21ml/yr (p=0.04). Treated group FEV1 % pred 62ml/yr vs 83ml/yr in the untreated group.

SIGN Quality Rating	-
Hierarchy of Evidence Grading	11b
NCC CC ID	1258