Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Managing Stable COPD
Inhaled bronchodilator therapy
Index

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Appleton S, Smith B, Veale A, Bara A. Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease. (Cochrane Review). *The Cochrane Library.Oxford:Update Software* 2003;**Issue 3**.	2003	1137
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Author / Title / Reference / Yr	Aalbers, R., Ayres, J., Backer, V., Decramer, M., Lier, P. A., Magyar, P., Malolepszy, J., Ruffin, R., & Sybrecht, G. W. 2002, "Formoterol in patients with chronic obstructive pulmonary disease: A randomized, controlled, 3-month trial", *European Respiratory Journal*, vol. 19, no. 5, pp. 936-943. Ref ID: 249
N=	N=692 randomised / N=576 completed. Geographical Location=86 centres in 9 countries. Duration 12 wks

Research Design	Randomised, double-blind, parallel-group study
Aim	Investigation of maintenance treatment
Operational Definition	Prebronchodilator FEV1 >0.7 L and 40-70% of predicted, FEV1/FVC ratio <89% pre normal.
Population	Moderate to severe COPD (Asthma excluded)
Intervention	Formoterol 4.5ug, 9um or 18ug twice daily.
Comparison	Placebo
Outcomes	Symptom scores / Use of relief medication / Spirometry / Shuttle walking test / Baseline and Transitional Dyspnoea Index / Safety
Characteristics	Age range 50-80 Current or former smokers Smoking history of at least 10 pack yrs 2 wk run-in period Inclusion criteria – Pts were not allowed inhaled and oral $beta_2$-agonist (apart from relief medication), inhaled anticholinergics, xanthine derivatives, leukotriene antagonists, medication containing ephedrine and parenteral glucocorticosteroids. Glucocorticosteroids were allowed throughout the study Pts who suffered an exacerbation of CPOD requiring medical intervention during the run-in period were excluded. Relief medication during run-in and throughout the study terbutaline sulphate 0.5mg.
Results	Symptom scores Total symptom score Formoterol 4.5ug, 9ug treatments were not statistically different from placebo. Formoterol 18ug demonstrated a significant reduction in total symptom score vs the placebo group (13% difference relative to placebo; 95%CI: 80-95; p=0.002) Individual symptoms Average scores for sleep disturbance, breathlessness, cough & chest tightness all decreased during formoterol treatment compared with placebo. Statistically significant improvements were seen with: Breathlessness Formoterol 9ug 93% difference relative to placebo; 95%CI: 87-98; p=0.0136 Formoterol 18ug 91% difference relative to placebo; 95%CI: 86-96; p=0.0014 Chest tightness Formoterol 9ug 89% difference relative to placebo; 95% CI: 83-95; p=0.0004 Formoterol 18ug 92% difference relative to placebo; 95% CI: 86-98; p=0.0099 Treatment days that were symptom free at the end of treatment Placebo group 7% treatment days were symptom free Formoterol 4.5ug, 21% days symptom free

	Formoterol 9ug, 71% days symptom free Formoterol 18ug, 86% days symptom free Difference compared with placebo was statistically significant for: Formoterol 9ug p=0.025 Formoterol 18ug p=0.006 Use of relief medication Formoterol 9ug and 18ug significantly reduced the need for relief medication compared with placebo (-18% and –25% respectively: p=0.008 and p<0.001). Spirometry All doses of formoterol produced statistically significant increases in FEV1 compared with placebo (p=0.010, 0.039 and 0.001 for the 4.5ug, 9ug and 18ug formoterol groups respectively. Shuttle walking test (SWT) There was considerable variation in baseline walking ability. The average increase in walking distance was small and of the same magnitude for all groups (no p values given). Baseline and Transitional Dyspnoea Index The mean BDI for the study population was 6.4 (scale 0-12). The TDI was statistically significant in the group treated with 18ug formoterol b.d. compared with the placebo group (p=0.002). Safety 28 serious adverse events were reported, 3 in the placebo group and 25 in the three formoterol groups. There were no significant differences between the groups treated with formoterol in terms of the number, type or intensity of events. Withdrawals 114 withdrawals from the study during the treatment 42 due to COPD deterioration 18 due to other adverse events 54 due to other reasons The overall withdrawal frequency was similar between the 4 groups (ranging from 16-19%) and there were no significant differences between the groups with respect to their survival distributions. Deterioration of COPD and respiratory infection were the two most commonly reported adverse events in all treatment groups.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	249

Author / Title / Reference / Yr	Appleton S, Smith B, Veale A, Bara A. Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease.(Cochrane Review). *The Cochrane Library.Oxford:Update Software* 2003;**Issue 3**.
N=	Eight RCTs 6 were parallel group studies of 12-16 wks 2 were crossover studies with four wk treatment arms N=2151
Operational Definition	Operational definition of classification severity not provided e.g. BTS/ ERS / GOLD. No baseline severity classification stated.
Population	Non-asthmatic subjects with COPD. Stable (no recent infections, exacerbations, hospitalisations in the past month) FEV1 75% or less than predicted, FEV1/FVC less than 70% predicted. Less than 15% reversibility of FEV1 after a dose of short acting beta$_2$-agonist.
Intervention	Salmeterol or formoterol
Comparison	Placebo
Outcomes	Lung function (FEV1 & PEF) Six minute walk test Health related quality of life (HRQL) Dyspnoea measurements including symptom diary scores Number of exacerbations Rescue salbutamol use
Characteristics	Characteristics table not provided Data provided for individual trials Individual FEV1 / FEV1/FVC given for each trial. FEV1 indicate that most pts had moderate COPD. Male / female split not given for all trials Mean age 62-65
Results	The Cochrane results are presented in two sections: i) Salmeterol 50mcg and ii) Salmeterol 100mcg, for twice daily versus placebo. Salmeterol 50mcg **Lung Function:** There was variation across studies in the reporting of FEV1. A significant increase in FEV1 was seen in the treatment group and the control group mean FEV1 worsened compared to baseline (WMD=0.1 litres, 95% CI: 0.05, 0.15). (Boyd 1997). Two parallel group studies reported baseline FEV1 at 12wks (Goodwin 1997, Mahler 1999) and pooled analysis demonstrated no significant treatment differences (WMD –0.07L, 95% CI: -0.21; 0.06) The parallel group study over 12 wks (van Noord 2000) reported an improvement in % predicted FEV1 (WMD=2.8%, 95% CI: 0.03, 5.57) in subjects treated with salmeterol compared to placebo.

	Pooled analysis of Boyd 1997, Goodwin 1997, Mahler 1999 and van Noord 2000, reporting three difference measures of FEV1 using the standardised mean difference for each study and a random effects model indicated no significant treatment effect (SMD 0.14, 95% CI –0.16 to 0.44). **Exercise Tolerance:** No significant difference was demonstrated in the mean change in distance walked from baseline (WMD=1.93 metres, 95% CI:-15.4, 19.26) Grove 1996. Mahler 1999 and Goodwin 1997 reported no significant difference between treatment and placebo groups in six minute walk distance (WMD=-0.5 metres, 95%CI:-29.5, 28.49). **Health Related Quality of Life:** St Georges Respiratory Questionnaire (SGRQ) Jones 1997 and R-van Molken 1999 used the SGRQ, a negative WMD indicates improvement and a positive WMD indicates worsening compared to baseline. Pooled analysis of change in SGRQ scores in Impacts and Total domains, demonstrated no significant response of any of the SGRQ domains Total, Symptoms, Activity and Impacts to treatment. (WMD Total=-2.93, 95% CI:-7.72, 1.86); (WMD Symptoms= -2.17, 95%CI: -6.08, 1.73); (WMD Activity=-0.74, 95% CI:-3.77, 2.28); (WMD Impacts=-4.25, 95%CI:-11.7, 3.19). Medical Short Form 36 (SF-36) General health showed significant improvement in only one of the eight components –Role Physical WMD-12.4 (95%CI:1.5, 23.3). Using the SF-36 a positive WMD indicates improvement and a negative WMD indicates worsening compared to baseline. The Chronic Respiratory Disease Questionnaire (CRQ) Three studies used the CRQ. R-van Molken 1999, Mahler 1999, Goodwin 1997. Pooled analysis of these three studies indicated that salmeterol treatment was not associated with improvements in any of the five CRQ domain scores. **Dyspnoea:** Mahler 1999 and Goodwin 1997 used the Transition Dyspnoea Index (TDI) to measure the change in severity of dyspnoea. No significant treatment difference was observed for this outcome (WMD=0.17, 95% CI:-0.46, 0.81). Borg dyspnoea scores were reported by Goodwin 1997, Mahler 1999 and Boyd 1997. There was no significant difference in mean pre-walk or post-walk Borg scores respectively (WMD=-0.05, 95%CI:-0.38, 0.28) and (WMD=-0.16, 95%CI:-0.59, 0.27). Boyd 1997 demonstrated that significantly more patients in the salmeterol group had Borg scores less than three, indicating moderate dyspnoea (OR=1.68, 95% CI: 1.13, 2.48). **Symptom Scores:** Van Noord 2000 reported that mean daytime symptom scores were significantly reduced by salmeterol treatment (WMD=-0.3, 95% CI:-0.58, -0.02) but not mean night time scores (WMD=0.10, 95% CI:-0.18, 0.38). Mahler 1999 and Goodwin 1997 found no significant differences in self-reported mean day and night time symptoms scores for dyspnoea, chest tightness and cough. Boyd 1997 reported statistically significant differences in the distribution of median day and night time symptoms scores between salmeterol and placebo.

	Ulrik 1995 reported median day and nighttime symptom scores to be significantly lower in the salmeterol treatment compared to the placebo period. **Exacerbations:** Salmeterol did not significantly affect the incidence of COPD exacerbations (OR=0.69, 95% CI: 0.47, 1.03). **Rescue bronchodilator use:** Van Noord 2000 reported that the % of days and nights with additional salbutamol use was significantly reduced in the salmeterol treated group (WMD=-40.0%, 95%CI: -54.61, -25.39) and (WMD=-16.0%, 95%CI: -29.61, -2.39) respectively. Mahler 1999 and Goodwin 1997 found that the mean number of daytime puffs of salbutamol demonstrated no significant differences in salbutamol use (WMD=-0.85, 95% CI: -1.80, 0.10) between salmeterol and placebo groups. Ulrik 1995 reported that the median number of nights without additional salbutamol use was significantly increased in the salmeterol group and that the median daytime salbutamol use was significantly different in salmeterol treated group ($p<0.001$). Night time % reduction in salbutamol use in salmeterol treated group was also significantly different ($p=0.014$) from the placebo treated subjects. **Salmeterol 100mcg** All data for outcomes was derived from the Boyd 1997, except for HRQL which was obtained from the Jones 1997) **Lung Function** FEV1 was significantly increased after 16wks of salmeterol treatment (WMD=0.12L, 95% CI: 0.07, 0.*17).* **HRQL** No significant improvement on salmeterol 100mcg. **Dyspnoea** Treatment with salmeterol did not result in a larger number of subjects with lower Borg breathlessness scores (OR=1.18, 95% CI: 0.79, 1.77). **Symptom Scores** Statistically significant differences in the distribution of median day and night time symptoms scores between salmeterol and placebo treated groups were reported. **Exacerbations** Salmeterol did not reduce the incidence of exacerbations (OR=0.98, 95% CI: 0.64, 1.52). Rescue salbutamol Use Median daytime salbutamol use was significantly different in the salmeterol treated subjects compared with placebo ($p<0.001$) and also nighttime % reduction in salbutamol use in salmeterol treated subjects was significantly different ($p=0.005$) from the placebo treated subjects.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
NCC CC ID	1137

Trial included	Van Noord 2000 (N=144), Goodwin 1997 (N=403), Van Molken 1999 (N=144), Mahler 1999 (N=411), Boyd 1997 (N=674), Jones 1997 (N283), Grove 1996 (N=29), Ulrik 1995 (N=63).

Author / Title / Reference / Yr	Boyd, G., Morice, A. H., Pounsford, J. C., Siebert, M., Peslis, N., & Crawford, C. 1997, "An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *European Respiratory Journal*, vol. 10, no. 4, pp. 815-821. Ref ID: 252 (Boyd 1997 paper included in Appleton S, Poole P, Smith B, Veale A, Bara A. Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease patients with poorly reversible airflow limitation (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.).
N=	N=674 / Duration=16wks / 75 Centres / 18 countries
Research Design	Multicentre, multinational, randomised, double-blind, parallel group study
Aim	To compare the efficacy and safety of salmeterol xinafoate 50 and 100ug twice daily
Population	Stable COPD
Intervention	Salmeterol xinafoate 50ug b.d. and 100ug b.d.
Comparison	Placebo
Outcomes	Symptom scores Lung function Exercise test Adverse events
Characteristics	Current or previous smokers / Ages 40-75yrs / Males=532 / Females=142 Concomitant medication included usual non-beta$_2$-agonist therapy. During the follow-up period pts could be prescribed bronchodilator medication Salbutamol used for symptomatic relief Medication use was comparable between treatment groups 2wk run-in period
Results	**There were no differences between the effects of salmeterol 50ug and 100ug.** Symptom Scores Significant improvement in daily symptom scores for patients taking either 50ug (p=0.043) or 100 ug (p=0.01) twice daily of salmeterol compared to placebo. There was a statistically significant difference in the distribution of the median daytime symptom scores between the 50ug salmeterol and placebo groups (p=0.043) and between the 100ug salmeterol and placebo groups (p=0.01). The 95% CI for the median difference were 0.00 – 0.00 in both cases.

	A statistically significant difference was observed in the distribution of median night time symptom scores between the 50ug salmeterol and placebo group, and between 100ug salmeterol and placebo group (p=0.001). The 95% CI for the median difference was 0.0 – 0.0 for both comparisons. Additional bronchodilator usage There was a statistically significant difference in the median day time use between each salmeterol group and placebo (p<0.001 in each case) in favour of salmeterol. Additional bronchodilator usage was also reduced at night, following a similar pattern. Lung function FEV1 measurements improved significantly in each salmeterol group. P values were significant for both treatment groups' 50ug and 100ug salmeterol at 1-4wks / 5-8wks / 9-16wks compared to placebo. (9-16wks for salmeterol 50ug (p<0.001) and salmeterol 100ug (p<0.001). Six minute walk and breathlessness No difference was observed between treatment groups for the distance walked in 6min, pts treated with salmeterol 50ug were significantly less breathless than those treated with placebo after 6 min walk, after 8wks (p=0.024) and 16 wks (p=0.004) Safety The incidence of pts who reported an adverse event considered to be related to the study medication was similar for placebo (18%) and salmeterol 50ug (16%) and salmeterol 100ug (24%).
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	252

Author / Title / Reference / Yr	Brusasco, V., Hodder, R., Miravitles, M., Korducki, L., Towse, L., Kesten, S. (2003). Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax*, 58, 399-404.
N=	Total N =1207 participants Location=not specified Duration=6 months Sites=18 countries
Research Design	RCT randomised, multi-center, double-blind, placebo-controlled, double dummy, parallel group design.
Aim	To compare tiotropium 18 ug once daily delivered by the HandiHaler and salmeterol 50 ug twice daily via a metered dose inhaler (MDI) in patients with COPD.
Operational Definition	Relatively stable airway obstruction: forced expiratory volume in 1 second (FEV1) <65% of predicted normal and <70% of forced vital capacity (FVC).

Population	Patients with relatively stable airway obstruction with forced expiratory volume in 1 second (FEV1) <65% of predicted normal and <70% of forced vital capacity (FVC), over 40 yrs of age, with a smoking history of >10 pack years.
Intervention	18 ug/d tiotropium by HandiHaler N=402 50 ug/2xd salmeterol via metered dose inhaler N=405
Comparison	Placebo N=400
Outcome	FEV1 and FVC Dyspnoea- (Baseline Dyspnoea Index and Transition Dyspnoea Index) HRQoL (St Georges Respiratory Questionnaire, SGRQ) Exacerbations (a complex of respiratory symptoms lasting at least 3 days and usually associated with a therapeutic intervention) Adverse events
Characteristics	Age tiotropium/salmeterol/placebo 63.8yrs/64.1yrs/64.6yrs % Male tiotropium/salmeterol/placebo 77.4/75.1/76.3 Duration of COPD yrs tiotropium/salmeterol/placebo 9.0/9.9/9.8 Smoking history (pack yrs) tiotropium/salmeterol/placebo 44.1/44.8/42.4 FEV1 tiotropium/salmeterol/placebo 1.12/1.07/1.09 FEV1/FVC % tiotropium/salmeterol/placebo 43.7/42.2/42.3 FEV1 % predicted tiotropium/salmeterol/placebo 39.2/37.7/38.7 FVC tiotropium/salmeterol/placebo 2.59/2.55/2.60
Results	**FEV1 and FVC** Evaluation of morning pre-dose FEV1, peak FEV1 and mean FEV1 (0-3 hours) showed that tiotropium was superior to salmeterol while both active drugs were more effective than placebo. **Health Related Quality of Life & Dyspnoea** A significant difference was observed for tiotropium versus placebo ($p<0.01$). The percentage of patients achieving an improvement of at least 4 units was 48.9%, 43.2% and 39.3% for the tiotropium, salmeterol, and placebo groups respectively ($p<0.05$ for tiotropium versus placebo). SGRQ total score improved by 4.2 (0.7), 2.8 (0.7) and 1.5 (0.7) units during the 6 month trial for the tiotropium, salmeterol and placebo groups, respectively ($p<0.01$) tiotropium vs placebo). Compared with placebo, TDI focal score improved in both the tiotropium group (1.1 (0.3) units, $p<0.001$) and the salmeterol group (0.7 (0.3) units compared with placebo ($p<0.05$), without a significant difference between the tiotropium and salmeterol groups ($p=0.17$). **Exacerbations** "Tiotropium significantly delayed the time to the first COPD exacerbation compared with placebo ($p<0.01$). The proportion of patients treated with at least one exacerbation was 32%, 35% and 39% in the tiotropium, salmeterol, and placebo groups, respectively ($p>0.05$). Patients treated with tiotropium had significantly fewer COPD exacerbations per patient per year than those treated with placebo ($p<0.05$)". "Patients treated with tiotropium had fewer hospital admissions related to COPD exacerbations than

	those treated with placebo or salmeterol. Patients treated with both tiotropium and salmeterol had fewer days in hospital for COPD than the placebo group. However, the difference between the treatment groups for both the number of hospital admissions and the number of days in hospital was not statistically significant." **Adverse events** Dryness of the mouth was the only event that was statistically higher with tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%). **Health resource and restricted activity** The number of days during which patients were unable to perform their usual daily activities was lowest in the tiotropium group (tiotropium 8.3 (0.8), salmeterol 11.1 (0.8), placebo 10.9 (0.8), $p<0.05$).
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ib
NCC CC ID	1790

Author / Title / Reference / Yr	Campbell, S. 1999, "For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base", *Archives of Internal Medicine 25 JAN 1999Vol 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 36µg plus albuterol 180µg 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 – 180ug 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)*

<table>
<tr><td>Outcome</td><td>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</td></tr>
<tr><td>Characteristics</td><td>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</td></tr>
<tr><td>Results</td><td>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
<table>
<tr><td></td><td>Combination therapy (n = 176)</td><td>Albuterol (n = 180)</td></tr>
<tr><td>Day 1 FEV1</td><td>0.37</td><td>0.29</td></tr>
<tr><td>Day 29 FEV1</td><td>0.34</td><td>0.27</td></tr>
<tr><td>Day 1 FVC</td><td>0.77</td><td>0.65</td></tr>
<tr><td>Day 29 FVC</td><td>0.71</td><td>0.61</td></tr>
</table>
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.</td></tr>
</table>

	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 to14. **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	- (Blinded double critical appraisal)
Hierarchy of Evidence Grading	1b
NCC CC ID	826

Author / Title / Reference / Yr	Casaburi, R., Briggs, D. D., Donohue, J. F., Serby, C. W., Menjoge, S. S., & Witek, T. J. 2000, "The spirometric efficacy of once-daily dosing with tiotropium in stable COPD - A 13-week multicenter trial", *Chest*, vol. 118, no. 5, pp. 1294-1302.Ref ID: 174
N=	N=470. Duration=13wks. Geographical Location=USA. Sites= multicentre (25)
Research Design	Randomised, double blind, placebo controlled, trial
Aim	To compare the bronchodilator efficacy and safety of tiotropium and placebo.
Operational Definition	COPD as defined by ATS. FEV1 <65% of predicted normal values and an FEV1 <70% of FVC.
Population	Stable COPD (mean FEV1=38.6%). Outpatients. Asthma excluded
Intervention	Tiotropium 18ug (N=279) once daily by a dry power inhaler device.
Comparison	Placebo (N=191)
Outcomes	Spirometry evaluated on days 1, 8, 50 & 92. Primary bronchodilator efficacy end point was trough FEV1 response on final treatment visit (day 92). Long-term effectiveness was evaluated by comparing treatment and placebo groups; mean weekly PEFR / symptom scores /

	physician global evaluation scores and “as needed” albuterol.
Characteristics	Age average 65yrs Male 65% Ethnic origin 92% white Overall FEV1 at baseline was 1.02 L, mean predicted 39%, mean FEV1/FVC ratio 46%. Concomitant medication – Allowed to use albuterol metered dose inhaler as needed, stable doses of theophylline, inhaled corticosteroids and the equivalent of <10mg/d of oral prednisone throughout the study. To ensure standardised conditions on pulmonary function tests pts discontinued treatment with theophylline preparations for 24h. Treatment with albuterol & inhaled corticosteroids was stopped at least 12h pre testing.
Results	**Efficacy FEV1 & FVC** Tiotropium compared to placebo demonstrated a statistically significant increase in both FEV1 and FVC after first dose ($p<0.001$) and response after 3/12 therapy ($p<0.001$). Trough FEV1 for tiotropium remained 10-13% greater than baseline throughout the 13wk treatment. Tiotropium average FEV1 response during first 3hr after dosing was 0.16 L greater than pre dose baseline on the first day of dosing and the average increase ranged from 0.20-0.21 L greater than baseline for the 13wk study. All FEV1 responses were significantly greater than placebo ($p<0.001$). In all FVC comparisons, the difference between tiotropium and placebo was statistically significant ($p<0.001$). **Physician’s Global Assessment and Symptoms** For pts receiving tiotropium, physician global evaluations on test days were significantly improved ($p<0.001$) compared to placebo for the 13wk study period. Symptom scores showed a significant difference favouring tiotropium vs placebo for wheezing and shortness of breath ($p<0.01$) but not for tightness of the chest or cough. **Supplemental Albuterol Use** Albuterol use was maintained in the placebo group where as use decreased approximately 30% in the first wk and remained at this level in the tiotropium group. The difference in albuterol use between the two treatment groups was significant ($p<0.001$) at all 13wks. All other respiratory concomitant medication use was similar for the two groups during the treatment period. **Safety** 62% of the pts in the tiotropium group compared to 67% of pts in the placebo group reported adverse events. There was a trend for fewer COPD exacerbations in the tiotropium group (16% vs 22%) but the difference in proportions was not significant. There was one fatality in the tiotropium group (cardiac arrhythmia) the pt had a history of cardiovascular disease; PM was declined by the family. No differences were noted between groups for changes in lab values, ECGs or physical examinations.
SIGN Quality Rating	+

Hierarchy of Evidence Grading	1b
NCC CC ID	174

Author / Title / Reference / Yr	Casaburi, R., Mahler, D. A., Jones, P. W., Wanner, A., San Pedro, G., ZuWallack, R. L., Menjoge, S. S., Serby, C. W., & Witek, T. 2002, "A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease", *European Respiratory Journal*, vol. 19, no. 2, pp. 217-224. Ref ID: 34
N=	N=921. Duration=1yr. Multicentre=50 clinical centres
Research Design	Two identical clinical trials. Double blind, placebo controlled
Aim	Evaluation of the long-term safety and efficacy of tiotropium
Operational Definition	Clinical diagnosis of COPD as defined by the ATS. Participants were required to have a FEV1 of <65% of predicted normal values and <70% of FVC.
Population	Stable COPD (Asthma excluded). (Some COPD exacerbations included "only those COPD exacerbations recorded as adverse events were used for comparison in order to eliminate day-to-day fluctuations in symptoms").
Intervention	Tiotropium 18ug once daily via a dry powder inhaler device
Comparison	Placebo
Outcomes	Lung function / Symptoms / Health outcomes / Generic health status / Medication use / Adverse effects
Characteristics	Pts were permitted an albuterol metered dose inhaler, as needed, stable doses of theophylline, inhaled glucocorticosteroids and the equivalent of <10mg day oral prednisone throughout the study period. (In order to standardise conditions on spirometric test days, pts discontinued theophylline 24hrs prior to spirometric testing albuterol and inhaled corticosteroids were stopped >12h prior to spirometric testing). Age= 65yrs average Sex = 65% Male Ethnic origin = Not stated Mean FEV1 at screening visit was = (Presented in baseline characteristics table for treatment and placebo groups separately. Tiotropium group results are cited in this Evidence Table, placebo group virtually identical) = FEV1 L 1.04, FEV1 % pred 39.1, FVC L 2.31, FEV1/FVC% 45.8.

Results	**Spirometry** Tiotropium demonstrated statistically significant bronchodilation relative to placebo for trough FEV1 response (12% over baseline) ($p<0.01$) and mean response during the 3h flowing dosing (22% over baseline) ($p<0.001$) over 12 months. FVC responses paralleled those of FEV1. **Symptoms** Tiotropium group showed less dyspnoea ($p<0.001$) at all time points over 12 months. COPD symptom scores showed statistically significant improvements for shortness of breath and wheezing ($p<0.05$) but not for cough and chest tightness, compared with placebo. **Health outcomes** *Exacerbations* Proportion of pts experiencing at least one COPD exacerbation was lower in the tiotropium group (36%) than in the placebo (42%) (14% reduction, $p<0.05$). There were significantly fewer exacerbations in the tiotropium group compared to the placebo group that constituted a 20% reduction ($p=0.045$). Pts on tiotropium spent significantly fewer days in hospital for exacerbations compared with placebo that constituted a 50% reduction ($p=0.023$). *Disease Specific SGRQ* The tiotropium group demonstrated a statistically significant improvement in total score compared to those in the placebo group ($p<0.05$). *Generic health status (SF-36)* The tiotropium group demonstrated improvement in physical health domains relative to placebo on all assessment days ($p<0.05$) *Medication Use* During the last wk of the trial, mean albuterol use was 3.2 and 4.1 doses/day^{-1} in the tiotropium and placebo groups respectively (p 0.01). *Physician Global Assessment* Patients in the tiotropium group showed greater improvement in global evaluation than those in the placebo group on all test days ($p<0.01$). Adverse Events Adverse events were comparable with placebo, except for dry mouth incidence (tiotropium 16% versus 3%, $p<0.05$). Less than 1% withdrew for this event. There were no significant differences in the proportion of pts with serious adverse events, in those withdrawing for adverse events or in deaths.
SIGN Quality Rating	+
Hierarchy of Evidence	1b

Grading	
NCC CC ID	34

Author / Title / Reference / Yr	Colice, G. L. 1996, "Nebulized bronchodilators for outpatient management of stable chronic obstructive pulmonary disease", *American Journal of Medicine*, vol. 100, no. 1 A, pp. 1A11S-1A18S. Ref ID: 326
N=	N=223 Centres=11 Duration=12wks Location=USA
Research Design	Randomised, double blind, parallel group, trial.
Aim	To compare the efficacy, safety and persistence of effect of either ipratropium or albuterol given by home nebuliser.
Operational Definition	FEV1 <65% predicted and an FEV1<70% of FVC
Population	Stable COPD (asthma excluded)
Intervention	500ug ipratropium 0.1% inhalation solution (delivered via compressor driven nebuliser via mouthpiece over 15/mins)
Comparison	2.5ug albuterol inhalation solution. (Same delivery mode)
Outcomes	**Test times** Long test days were carried out on day 1, 43 and 85. Spirometry was repeated at 15, 30mins and hourly for 8 hrs. QoL question was given between the second and third hours **Outcomes** Primary efficacy analyses FEV1 & FVC / onset of 15% increase in FEV1 / duration of a 15% increase from baseline / time to peak response. Secondary efficacy variables were Physician's global evaluation / QoL.
Characteristics	Concomitant medications – excluded if cromolyn sodium or large doses of corticosteroids. Regular use of non-study inhaled bronchodilators was not allowed during the trial. However, inhaled beta$_2$-agonists could be used on an as-needed basis. Pts were not allowed to use theophylline preparations for 24 hrs, long acting bronchodilators for 18 hrs and SA bronchodilators and either inhaled or oral corticosteroids for 12 hrs prior to pulmonary function lab tests. Average Age=64yrs Sex=Male / female split not detailed Ethnic origin= Not detailed Mean FEV1 at screening visit was 1.02 L for ipratropium and 0.99 L for albuterol.
Results	**Lung function** FEV1 response was similar for both drugs on (Peak increases of 33% after ipratropium and 36% after albuterol). However, albuterol effect on FEV1 decreased over time. No p values given. Ipratropium tended to have a delayed median onset of effect and time to peak effect but to have a longer duration of effect than albuterol. However, there were no consistently significant p values.

	There were no clinically or statistically significant differences between the two study drugs in either morning or evening PEFR. **Quality of Life** Statistically significant differences favouring ipratropium were found on day 43 for dyspnoea and fatigue and day 85 for emotional function. No p values given. **Physician's Global Evaluations** Scores were significantly higher in the ipratropium group from the 4 wk point to the end of the study. No p values given. **Adverse Events** There were no statistically significant differences for either study drugs. No deaths occurred. **Pulse and BP** There were no significant changes noted in either group.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	326

Author / Title / Reference / Yr	Cook,D.; Guyatt,G.; Wong,E.; Goldstein,R.; Bedard,M.; Austin,P.; Ramsdale,H.; Jaeschke,R.; Sears,M. 2001 Regular versus as-needed short-acting inhaled beta$_2$-agonist therapy for chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine*. Vol. 163, No. 1, pp. 85-90.
N=	N=73 recruited / N=62 completed run-in / N=53 completed the study. 73% of individuals recruited into the study are included in the analysis. Geographical Location= Respiratory practices and rehabilitation programs in Hamilton and Toronto, Ontario. Duration 6/12
Design	Randomised, double blind crossover trial One treatment period: Pts self-administered albuterol in addition to open-label albuterol as needed. Second treatment period: Pts received matching placebo in addition to open-label albuterol as needed.
Population	Moderately severe COPD (including exacerbations)
Intervention	Regular inhaled albuterol 100ug, 2 puffs four times daily
Comparison	Placebo
Outcomes	Spirometric measures / Peak flow / Functional exercise capacity / Health related QoL
Characteristics	Age >50yrs (average age 69yrs, age range not provided) 40% females Smoking history of >20 pack yrs FEV1< 70% predicted and FEV1/VC ratio of <0.7 after inhalation of 200ug albuterol

	Asthma excluded. **All pts received:** Regular ipratropium bromide at 20ug per puff in 2 puffs four times daily Beclomethasone at 250ug per puff or equivalent corticosteroids Open-labelled inhaled albuterol as needed
Results	Spirometric measures and peak flow rates There were not significant treatment effects and results were very similar whether pts were taking active or placebo medication. **6 min walk distance, dyspnoea and QoL** There were no statistically significant results between active and placebo periods. Symptoms Effect of albuterol on symptoms showed no evidence of a treatment effect. Amount of albuterol Pts taking regular albuterol used twice as much albuterol as during the placebo period, at an average of 12.8 puffs of active albuterol daily, whereas pts taking as-needed albuterol used an average of 6.3 puffs of active albuterol daily. Open-label use of albuterol was 1.7 puffs per day more during as needed use, but overall albuterol use was halved. Pts did not use the study inhaler less often during placebo than during active-treatment period. Primary finding – pts with COPD treated with inhaled ipratropium and corticosteroids do as well by using as needed inhaled albuterol as by using regular albuterol and require considerably less medication.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	129

Author / Title / Reference / Yr	Dahl, R., Greefhorst, L. A. P. M., Nowak, D., Nonikov, V., Byrne, A. M., Thomson, M. H., Till, D., & Della Cioppa, G. 2001, "Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease", *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 5, pp. 778-784. Ref ID: 171
N=	N=780. Duration 12 wks. Outpatients. Multicentre (number of sites not specified)
Research Design	RCT
Operational Definition	Diagnosis of COPD as per ATS
Population	COPD (including exacerbations)
Intervention	Formoterol 12ug (F12) + placebo twice daily Formoterol 24ug (F24) + placebo twice daily

	Ipratropium 40ug (IPR) + placebo four times daily Placebo (PL) + placebo
Comparison	Placebo - As above
Outcomes	FEV1 Symptoms Quality of Life Safety profile
Characteristics	Aged >40yrs Current or ex smokers > 10 pack yrs Males=582 / Females=198 Excluded asthmatics Concomitant medications: Inhaled corticosteroids used by approximately 50% in each of the four groups. B2 agonists were used by approximately 22% in each of the four groups. Antibiotics used by approximately 13% in each of the four groups. Pts on stable inhaled corticosteroid treatment were allowed to remain on that treatment throughout the trial. Rescue medication with inhaled salbutamol was allowed through out the study up to a maximum of 8 puffs/d. Short courses of antibiotics, oral corticosteroids and / or O2 were permitted in case of exacerbation or respiratory infection. Pts who needed additional medications for COPD were withdrawn from the study.
Results	Formoterol 12ug, formoterol 24ug and ipratropium 40ug significantly increased the FEV1 in comparison to placebo (all $p<0.001$) Formoterol 12ug and formoterol 24ug were significantly superior to ipratropium (all $p<0.025$) When compared to placebo, formoterol 12ug and formoterol 24ug significantly improved symptoms (all $p<0.007$) and quality of life ($p<0.01$ for total scores). Ipratropium did not show significant effects (all $p>0.3$). All study treatments exhibited a similar safety profile.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	171

Author / Title / Reference / Yr	Donohue, J. F., van Noord, J. A., Bateman, E. D., Langley, S. J., Lee, A., Witek, T. J., Kesten, S., & Towse, L. 2002, "A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol", *Chest*, vol. 122, no. 1, pp. 47-55. Ref ID: 137
N=	N=623 Duration=6/12 Location=12 countries Centres=39
Research Design	Randomised, placebo-controlled, double-blind, double-dummy, parallel-group study
Aim	Examine the efficacy and safety of tiotropium and salmeterol
Operational Definition	FEV1<60% of predicted normal and FEV1<70% of FVC.
Population	Stable COPD (Asthma excluded)
Interventions & Comparisons	Tiotropium 18ug or placebo capsules received once daily / salmeterol 50ug or placebo metered dose inhaler (MDI) received twice daily
Outcomes	Spirometry / Transition Dyspnoea Index (TDI) / St George's Respiratory Questionnaire (SGRQ)
Characteristics	All previous inhaled anticholinergic or LABA medication was discontinued. All pts received salbutamol MDI for as need rescue use. Age 65yr (mean) Sex 75% Male Ethnic origin Mean FEV1 at screening visit was 1.08 +/- 0.37 L, % predicted 40 +/- 12%
Results	Compared with placebo treatment, the mean pre dose morning FEV1 following 6/12 treatment increased significantly more for the tiotropium group (0.14 L) than the salmeterol group (0.09 L) p<0.01. The average FEV1 for tiotropium was statistically superior to salmeterol (difference 0.08 L: p<0.001). Tiotropium group TDI focal score was statistically significant compared to placebo (p=0.01). There was no significant change in this score for the salmeterol group. Tiotropium was also statistically superior to salmeterol in improving TDI focal score (p<0.05). At 6/12 the SGRQ total score for tiotropium vs. placebo was statistically significant at p<0.05. (Salmeterol vs. placebo p=0.4). Both active drugs reduced the need for rescue salbutamol (p<0.0001) There were no statistically significant differences in the number of exacerbations between groups. Other than dry mouth (10%) in the tiotropium group there were no significant differences among treatment groups. There were no deaths in the tiotropium group. Three deaths occurred in the salmeterol group, and four deaths in the placebo group. Study medication assessment of compliance not discussed.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	137

Author / Title / Reference / Yr	Grove, A., Lipworth, B. J., Reid, P., Smith, R. P., Ramage, L., Ingram, C. G., Jenkins, R. J., Winter, J. H., & Dhillon, D. P. 1996, "Effects of regular salmeterol on lung function and exercise capacity in patients with chronic obstructive airways disease", *Thorax*, vol. 51, no. 7, pp. 689-693. Ref ID: 265
N=	N=29. Duration=See under research design. Location= UK. No of Sites=Respiratory Outpatient Clinic
Research Design	Randomised, double blind, placebo controlled, crossover design. Spirometry tests were performed during the first hr after the first dose and again 6hrs after dosing. At the end of the 4 wk treatment period measures were taken 6hrs after the final dose of study medication. Pts then had a one wk washout period before crossing over to the second treatment period.
Aim	To evaluate the effects of single and chronic dosing with salmeterol
Operational Definition	FEV1 of 25-75% of predicted normal and 5-15% reversibility
Population	Stable COPD
Intervention	Salmeterol 50ug twice daily for 4wks by MDI followed by placebo (N=15)
Comparison	Placebo followed by salmeterol (N=14) as above
Outcomes	Exercise capacity Lung function
Characteristics	Pts with significant systemic or musculoskeletal disease or those requiring maintenance therapy with oral steroids were excluded. Concurrent medication included inhaled corticosteroids (N=24) theophylline (N=6) and inhaled anticholinergics (N=7). Prior to run in 28 pts were using inhaled $beta_2$-agonist. No demographic table available however results state that there was no significant difference in baseline lung function values – FEV1 42 (3%) of predicted, and 5-15% reversibility. Mean age 64yrs. Range not documented. Male / female ratio 22 men / 7 women
Results	Salmeterol produced a small increase in FEV1 at 1 and 6 hrs after a single dose and this was maintained after chronic dosing: Single dose 1hr; mean difference 0.07 (95% CI 0.02 to 0.11) L. Single dosing at 6 hrs; mean difference 0.16 (95% CI 0.09 to 0.22) L. Chronic dosing at 6 hrs; mean difference 0.11 (95% CI 0.03 to 0.19) L. The increase in FVC was greater in salmeterol than with placebo @ 6 hrs after the single dose but not the chronic dosing; single dose at 6hrs 0.17 (95% CI 0.04 to 0.29) L. There were no significant differences in exercise capacity after single or chronic dosing with salmeterol compared with placebo. Borg score for perceived exertion following the 6 minute walk after chronic treatment with salmeterol compared with placebo were

	significantly lower p=0.004 but not for single dosing (p=0.06)
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	265

Author / Title / Reference / Yr	Jones, P. W. & Bosh, T. K. 1997, "Quality of life changes in COPD patients treated with salmeterol", *American Journal of Respiratory and Critical Care Medicine*, vol. 155, no. 4, pp. 1283-1289. Ref ID: 180
N=	7 countries (chosen because of the availability of questionnaires in respective languages) 16 wks duration
Aim	To quantify changes in Health Related Quality of Life after treatment with salmeterol beta$_2$-agonist in patients with COPD. Pts recruited to this quality of life study formed a cohort taking part in a larger study comparing two doses of salmeterol 50ug twice a day and 100 ug twice daily, with placebo.
Operational Definition	Less than 15% reversibility of FEV1 following salbutamol
Population	COPD
Intervention	Salmeterol, 50ug or 100ug twice daily by metered-dose inhalers
Comparison	Placebo
Outcomes	St. George's Respiratory Questionnaire (SGRQ) Medical Outcomes Study Short Form 36 (SF-36) Completed at the end of the run-in period and after 16wks of treatment
Characteristics	All three groups were well matched in terms of baseline demographic data and concomitant medication. Mean age 62yr Age range 40–70yrs 79% male 2wk run in period prior to randomisation. Current therapy was permitted with the exception of oral or inhaled beta$_2$-agonist therapy. Salbutamol by metered dose-inhalers provided throughout the study for use as necessary to relieve symptoms.
Results	SGRQ **Salmeterol and placebo** Compared with placebo, salmeterol 50ug twice daily was associated with significant improvements in SGRQ: Total score p<0.001

	Impact score p<0.001 There were no differences between the results of pts receiving salmeterol 100ug twice daily and placebo. Salmeterol 50ug and 100ug There were significant differences in the responses to the two doses of salmeterol. Changes in SGRQ scores with salmeterol 50ug twice daily were significantly greater than with salmeterol 100ug: Total score p=0.01 Impact score p=0.004 SF-36 Salmeterol and placebo P values are not presented for salmeterol dosages compared to placebo. Salmeterol 50ug and 100ug There was a significant differences due to a worsening of health score with salmeterol 100ug and an improvement with salmeterol 50ug within the SF-36 components were: Physical functioning p=0.01 Role-physical p=0.004 Role-emotional p=0.007 Vitality p=0.002 FEV1 There was a significant difference in FEV1 after 16 weeks within the salmeterol 50ug group p<0.02 Concomitant steroid use There was no difference in response in any variable between those receiving and those not receiving concomitant steroids (p>0.1 in all cases)
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	180

Author / Title / Reference / Yr	Kaushik, M. L., Kashyap, S., Bansal, S. K., & Sharma, A. 1999, "Effectiveness of salmeterol in stable COPD", *Indian Journal of Chest Diseases & Allied Sciences*, vol. 41, no. 4, pp. 207-212. Ref ID: 269
Research Design	RCT described as double blind, randomized, placebo controlled.
N=	N=30. Duration 7 days. Geographical Location= India
Operational Definition	Severity of COPD disease not stated (e.g. mild, moderate, severe)

Population	Stable COPD
Intervention	N=15 Salmeterol 50ug twice daily two puffs
Comparison	N=15 Placebo
Outcomes	FEV1 / Walking distance / Breathlessness
Characteristics	Mean age 59yrs salmeterol group and 54yrs placebo group / 13 males / 2 females. Demographic / characteristics table not provided. Concomitant medication during study not discussed (state not on steroids or bronchodilator drugs at the time of entering trial).
Results	The mean maximum increase was noted on the day 7, which was 29.5% of baseline value ($p<0.05$) (details in main text of paper, different from abstract states 29.2% of baseline). The peak effect in terms of FEV1 was at 3 hrs after inhalation of salmeterol on all the 3/7 ($p<0.05$). No p values provided for walk test or breathlessness scores.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	269

Author / Title / Reference / Yr	Littner, M. R., Ilowite, J. S., Tashkin, D. P., Friedman, M., Serby, C. W., Menjoge, S. S., & Witek, T. J. 2000, "Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease", *American Journal of Respiratory and Critical Care Medicine*, vol. 161, no. 4, pp. 1136-1142. Ref ID: 176
N=	N=169. Duration=29days. Geographical Location= USA.
Research Design	Multicenter (9), randomised, double-blind, parallel group, placebo-controlled study.
Aim	Evaluation of the efficacy & safety of multiple dosing of tiotropium
Operational Definition	COPD defined as stable, moderate to severe airway obstruction with an FEV1 >30% and <65% of predicted normal and an FEV1 to FVC ratio of <70%. Reversibility of obstruction in response to any bronchodilator was not required.
Population	Stable COPD (Asthma excluded)
Intervention	Tiotropium 4.5ug, 9ug, 18ug or 36ug once daily at noon for 4wks. Dry power inhalation device.
Comparison	Placebo
Outcomes	Study comprised of 10 visits. Medication administered in clinic followed by testing at hourly intervals for 6hrs. FEV1 / FVC Safety

Characteristics	Concomitant medications allowed during the study included SA β agonists on an as needed basis. Theophylline & inhaled glucocorticosteroids were allowed. These medications were washed out for 12-24 hrs before testing on pulmonary function test days. Oral glucocorticosteroids were prohibited throughout the study. Anticholinergic drugs were not allowed during the treatment or post treatment periods. LA inhaled bronchodilators (salmeterol), oral β agonists and cromolyn sodium were not allowed during the study. Use of concomitant medication was similar across all groups Mean age 66yrs 57% male 95% Caucasian Mean FEV1 at screening visit was 1.08L (42% predicted).
Results	FEV1 / FVC *Single dose response* - All doses of tiotropium provided significant improvements in FEV1 compared with placebo ($p<0.05$). Multiple dose response All four doses of tiotropium provided a greater trough response than did placebo ($p<0.05$). Trough FEV1 increased after 1wk of daily administration and then remained greater than placebo throughout treatment. (No p values). 2-3wks after cessation of treatment the FEV1 response for all doses of tiotropium returned to baseline, but never fell below baseline (no evidence of rebound deterioration). (No p values). FVC response paralleled the FEV1 response. ***Safety*** The overall safety profile for the four doses of tiotropium was similar to placebo. There were no dose dependent increases in adverse events. Proportion of pts with adverse events: Placebo 37%, 4.6ug tiotropium 29%, 9ug tiotropium 18%, 18ug tiotropium 30% and 36ug tiotropium 50%. There were no clinically significant effects of tiotropium on vital signs.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	176

Author / Title / Reference / Yr	Mahler, D. A., Donohue, J. F., Barbee, R. A., Goldman, M. D., Gross, N. J., Wisniewski, M. E., Yancey, S. W., Zakes, B. A., Rickard, K. A., & Anderson, W. H. 1999, "Efficacy of salmeterol xinafoate in the treatment of COPD", *Chest*, vol. 115, no. 4, pp. 957-965. Ref ID: 37.
N=	N=411 Duration=12wks Location=USA. Sites=27
Research Design	Stratified, randomised, double blind, double dummy, placebo controlled, parallel group, clinical trial.
Aim	To compare the efficacy and safety of salmeterol xinafoate with inhaled ipratropium bromide and inhaled placebo.
Operational Definition	COPD diagnosis as defined by ATS. A baseline FEV1 of > 0.70 L & <65% of the predicted normal values or, if <0.70 L, >40% of predicted normal value and FEV1/FVC ratio of <70%
Population	COPD (Asthma excluded)
Intervention	Inhaled salmeterol 42ug twice daily Ipratropium 36ug four times daily
Comparison	Placebo
Outcomes	Pulmonary function, Dyspnoea rating (both primary efficacy measures) / HRQL / Safety Evaluations
Characteristics	Treatment with theophylline and SA bronchodilators was stopped 36 & 6 hr respectively prior to initiating study treatment. During the treatment period, pts on a stable regimen of oral <10mg prednisone per day or inhaled corticosteroids continued these regimens. Albuterol was allowed for acute symptomatic relief. Concomitant medication not broken down for groups Age= 63yrs Sex= 74% male Ethnic origin=92% white
Results	***N.B.*** *Main paper targets salmeterol intervention hence results / p values focused throughout the paper on salmeterol significant outcomes rather than ipratropium.* **Pulmonary Function Tests** (FEV1 measurements from 0 to 12 hrs over four 12 hr visits). *FEV1* The FEV1 response to a single dose of salmeterol at each time interval was significantly superior to two doses of ipratropium at hrs 4 and 6 at week 0 and at hrs 0, 4 and 6 at wk 12. The mean change from baseline for FEV1 demonstrated that salmeterol was statistically superior to ipratropium at wks 4 & 8 ($p<0.005$). Within the ipratropium group, change from baseline was significant ($p<0.026$) for all serial assessments except for hr 0 (pre dose) at day 84). *FVC* Changes from baseline for FVC in the ipratropium group were significant at all time points during all treatment wks except for hr 6 and hr 12 at wk 4 and hr 6 at wks 8 & 12 (doesn't state whether this was in comparison to salmeterol or placebo groups. No p value

	found). **Dyspnoea Ratings** *TDI* For all pts, statistically significant improvements for salmeterol and ipratropium vs placebo were observed at wks 2, 4, 8, and 10, and for ipratropium vs placebo also at wks 6 & 12. Over the 12 wk period there were no significant changes in the pre walk or post walk dyspnoea scores or the 6MW distance for any treatment group except at wk 10 when there was a statistically significantly increase in the ipratropium group compared to the placebo group ($p<0.018$). **Patient Self Assessment** Mean baseline daytime symptom scores (shortness of breath, chest tightness and cough) were not significantly different among treatment groups). No discussion of mean baseline night time symptom scores (Night time SOB only discussed favouring the salmeterol group). **Albuterol Supplemental Use** There was a significant decrease in mean puffs per days of albuterol in the salmeterol ($p<0.001$) and in the ipratropium ($p<0.047$) groups compared with placebo at every interval. **Exacerbations** % of pts experiencing one or more exacerbations over the 12wk treatment period were 33% placebo, 21% salmeterol and 31% ipratropium. No p values are discussed. Analysis of the time to first COPD exacerbation demonstrated salmeterol to have a delayed onset of exacerbations compared with placebo ($p=0.0052$) and ipratropium ($p=0.0411$). **Health Related Quality of Life** At wk 12, the mean CRDQ overall score was significantly higher for salmeterol ($p=0.007$) and ipratropium ($p=0.007$) than for placebo. The proportion of pts who achieved an increase of >10 points in overall score was significantly higher at wk 12 in the salmeterol (46% $p=0.002$) and ipratropium (39%, $p=0.041$) groups than placebo (27%). **Safety** No major differences were seen in the incidence of adverse events across treatment groups
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	37

Author / Title / Reference / Yr	Rennard, S. I., Anderson, W., ZuWallack, R., Broughton, J., Bailey, W., Friedman, M., Wisniewski, M., & Rickard, K. 2001, "Use of a long-acting inhaled beta$_2$-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease", *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 5, pp. 1087-1092. Ref ID: 173
N=	N=405 Duration=12wks Location=USA
Research Design	Randomised, double blind, placebo-controlled, parallel-group study
Aim	Evaluation of salmeterol compared with ipratropium and placebo.
Operational Definition	FEV1 of >0.70 L and < 65% of predicted, and an FEV1/FVC ratio of < 70% at initial screening. Pts with an FEV1 <0.70 L were eligible if the FEV1 was >40% of predicted.
Population	COPD (no explicit statement made re exclusion of asthmatics). Includes some exacerbation (see characteristics section)
Intervention	Salmeterol 42ug twice daily (inhalation aerosol)
Comparison	Ipratropium bromide 36ug four times daily Placebo
Outcomes	Primary efficacy end points were FEV1 / Baseline Dyspnoea Index (BDI) / Transitional Dyspnoea Index (TDI) Pulmonary function (spirometry & diffusing capacity), 6 min walk and Borg dyspnoea assessment, symptoms scores / QoL / Adverse events
Characteristics	Discontinued use of theophylline, ipratropium (except in the ipratropium treatment group) and oral β-agonists for the duration of the study. Oral corticosteroid therapy greater than the equivalent of prednisone at 10mg/d was excluded. Pts using inhaled corticosteroids at entry must have maintained a stable regimen for the duration of the study. Exacerbations during baseline or requiring parenteral steroids or were hospitalised were withdrawn. Treatment of exacerbations with oral corticosteroids for 14 days or less was permitted without withdrawing Average age=62yrs Sex=64% Male Ethnic origin= 70% white

Results	**N.B.** *Main paper targets salmeterol intervention hence results / p values focus throughout the paper on salmeterol significant outcomes rather than ipratropium.* **FEV1& FVC** FEV1 & FVC significantly improved with both salmeterol and ipratropium compared with placebo on Day1 of treatment (no p value given). Salmeterol had a significantly longer duration of action than ipratropium, whereas the onset of response to ipratropium was significantly faster (no p values provided). FEV1 & FVC responses to both salmeterol and ipratropium were significantly greater than placebo ($p<0.001$) for albuterol-responsive and albuterol-non-responsive groups (stratified at baseline). **Rescue Therapy** The numbers of puffs of rescue MDI are decreased in both the salmeterol and ipratropium groups. No p values given. **Symptoms** The mean distance walked did not increase by more than 10 yd for any treatment group during the 12 wk treatment period. There were no significant differences between treatment groups in post walk scores at the end of the study period. BDI scores demonstrated no significant differences between the three groups. During the early wks of treatment (not defined) significant improvement ($p<0.005$) of dyspnoea (TDI) occurred for both salmeterol and ipratropium groups compared with placebo. Significance was lost by wk 6 because of improvement of dyspnoea in the placebo group. **Exacerbations** % of pts experiencing one or more COPD exacerbations over the 12 wk treatment period were; placebo 30%, salmeterol 29% and ipratropium 27%. 20 pts (15%) in the placebo group experienced their fist exacerbation during wk1 compared with 6pts (5%) in the salmeterol group and 6 pts (4%) in the ipratropium group ($p<0.0005$ for actives vs placebo) **Health Status Measures** No statistically significant outcomes **Withdrawals** There were no significant differences between treatment groups in the proportion of pts who withdrew because of adverse events. There were no differences between ipratropium and placebo in withdrawals due to lack of efficacy or between salmeterol and ipratropium. **Adverse Events** There were no clinically significant differences in the incidence of adverse events across the treatment groups with the exception of events in the ear, nose and throat category. The incidences of these were greater for both salmeterol (n=58, p=0.0011) and ipratropium (n=58, p=0.031) compared to placebo (n=39).
SIGN Quality Rating	+
Hierarchy of Evidence	1b

Grading	
NCC CC ID	173

Author / Title / Reference / Yr	Rennard, S. I., Serby, C. W., Ghafouri, M., Johnson, P. A., & Friedman, M. 1996, "Extended therapy with ipratropium is associated with improved lung function in patients with COPD: A retrospective analysis of data from seven clinical trials", *Chest*, vol. 110, no. 1, pp. 62-70. Ref ID: 301
N=	N=1,445 Duration=90 days Location=USA
Research Design	Retrospective analysis of data from seven clinical trials from four drug development programmes; Atrovent aerosol, Atrovent solution, Combivent aerosol and Combivent solution. This is paper is not defined by the authors as either a systematic review or meta-analysis. Author states that similar study designs were used by the 7 trials and it was possible to pooled data from 1,445 evaluable pts.
Aim	To evaluate the effect of extended treatment with bronchodilators in pts with COPD.
Operational Definition	FEV1 of 65% or less of predicted normal in five of the seven trials or an FEV1 of 75% or less of predicted normal in two of the trials. In all trials the pts FEV1 had to be less than 70% of FVC.
Population	Moderately severe airflow obstruction (Asthma excluded)
Interventions & Comparisons	2x trials ipratropium inhalation aerosol with metaproterenol inhalation aerosol, 1x trial ipratropium inhalation solution with metaproterenol inhalation solution, 1x trial ipratropium inhalation solution with albuterol sulfate inhalation solution, 2x trials compared the combination of ipratropium bromide and albuterol sulfate by MDI with ipratropium inhalation aerosol alone and albuterol inhalation aerosol alone and 1 x trial compared the combination of ipratropium bromide and albuterol sulfate solution with ipratropium inhalation solution alone and albuterol sulfate solution alone. From the studies that included the combination therapy, only those pts treated with $beta_2$-agonist alone or ipratropium alone were included in the current analysis. Devices: 4x trials MDI, 3x trials nebuliser solutions.
Outcomes	FEV1 & FVC
Characteristics	Pts excluded if required more than 10mg prednisone daily and pts using cromolyn sodium. Concomitant medications – continued use of stable doses of theophylline, inhaled steroids and oral steroids (if not >10mg) was allowed during trials. Regular use of inhaled bronchodilators other than the study drugs was not permitted. Temporary increase or addition of oral corticosteroids during exacerbations limited to two periods of 5/7 each during the treatment phase of the trial. Lung function at baseline measured after with holding treatment with study medication for 12h and theophylline for 24 h both before and after the 90 day treatment period. Mean age range across all trials 61 – 66yrs Sex=88% Male

	Ethnic origin=Not specified Mean FEV1 at screening visits given separately for all 14 groups but not pooled. Range 0.880 – 1.166 L
Results	Limited results presented due to SIGN quality rating (sub analyses not presented). Changes in baseline function. Long-term therapy with ipratropium resulted in improvement in baseline FEV1 (28ml; $p<0.01$) and FVC (131ml; $p<0.01$) while long-term therapy with $beta_2$-agonist resulted in no significant change in FEV1 or FVC. In contrast, in the $beta_2$-agonist treated pts, there was minimal change in FEV1, decreasing 1ml ($p<0.2$) while FVC increased 20ml ($p>0.2$ compared with baseline). The changes following $beta_2$-agonist therapies were significantly less than those observed in the ipratropium treated pts for both FEV1 ($p<0.05$) and FVC ($p<0.01$). In each study, the ipratropium treated group did better after 90 days than the $beta_2$-agonist treated group.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	Does not fit Hierarchy of Evidence utilised by NICE. Retrospective analysis of data from seven clinical trials.
NCC CC ID	301

Author / Title / Reference / Yr	Rossi, A., Kristufek, P., Levine, B. E., Thomson, M. H., Till, D., Kottakis, J., & Della Cioppa, G. 2002, "Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD", *Chest*, vol. 121, no. 4, pp. 1058-1069. Ref ID: 966
N=	N=854 Duration=12 months Location=worldwide Sites=81
Research Design	Randomised, parallel-group, double blind, placebo controlled
Aim	As per title
Operational Definition	FEV1 <70% of the predicted value and >0.75 L, with anFEV1/vital capacity ratio of <88% of that predicted in men and <89%.
Population	COPD (Asthma excluded)
Intervention	12ug or 24ug formoterol (F12 & F24 respectively) twice daily via a single dose, breath activated inhaler
Comparison	Placebo or slow release theophylline (individualised doses – open label) twice daily
Outcomes	FEV1 measured @ 5, 15, 30 min, 1 h every hr up to 12hr following 3 &, 12 months of treatment FVC / pre dose REV1 @ all 3/12 visits / daily morning pre medication peak expiratory flow / daily total symptom score / daily number of puffs or rescue salbutamol / frequency of COPD exacerbations / QoL / Adverse events
Characteristics	Concomitant medications – inhaled corticosteroid treatment Short courses of antibiotics, oral corticosteroids and O2 were permitted with exacerbations. Rescue medication – inhaled salbutamol (up to 8 puffs day). Mean age=63yrs / Age range 34-88 / Sex=83% Males / Ethnic origin=Not detailed FEV1, L Mean=1.37 / range=0.5-3.9 FEV1 % predicted Mean=47 / range 19-75 FEV1/VC % Mean=49 / range 16-96

Results	**FEV1** Both F12 & F24 were superior to placebo whether or not the pts were receiving concomitant therapy with corticosteroids. The 12 h plots of mean FEV1 at 3/12 and 1yr demonstrated that compared to placebo, F12 & F24 improved post medication FEV1 at every time point and for each visit (all $p<0.001$). Theophylline was also significantly more effective than placebo at every time point and for each visit (all $p<0.05$). **Effect of treatment on morning pre medication FEV1** F12 & F24 were significantly more effective than placebo at every time point of the treatment period ($p<0.026$) with the exception of F24 at 9/12. Theophylline also significantly improved morning pre medication FEV1 over placebo during the entire treatment period ($p<0.013$). Both F12 and F24 were more effective than placebo with differences that were statistically significant ($p<0.001$ for both F12 & F24) at 3/12 and 1 yr. Significance levels for F12 compared to theophylline at 3/12 (p0.005) & 1yr (p0.026) Significance levels for F24 compared to theophylline at 3/12 (p0.002) & 1yr (p0.233) Significance levels for theophylline compared to placebo at 3/12 ($p<0.001$) & 1yr (<0.001) **FVC** At 12 hrs for 3/12 and 1yr of treatment showed that both F12 & F24 were significantly more effective than placebo (all $p<0.001$). Theophylline was significantly more effective than placebo (all $p<0.007$). Both F12 & F24 were superior to theophylline at 3/12 ($p<0.016$). **Diary Symptom Score** There was no statistical significance among the treatment groups. **Use of Rescue Medication** Both F12 and F24 produced reductions in the use of rescue medication over the whole treatment period in comparison to placebo (all $p<0.003$). **COPD Exacerbations** The mean % of bad days averaged over 3/12 preceding each visit at 3, 6, 9, and 12 months. Both F12 & F24 were significantly superior to placebo ($p<0.008$) and to theophylline ($p<0.035$), while there was no significant difference between theophylline and placebo ($p=0.617$). The number of COPD related hospitalisations (severe COPD exacerbations) was four times higher in the placebo group than in the F24 group. Marked differences were also seen in the comparisons between the placebo group and the F12 groups and the theophylline group. **QOL** Compared to pts receiving placebo, those receiving both F12 and F24 showed statistically significant improvement in the total SGRQ score at the end of the treatment period ($p=0.030$ and $p=0.009$ respectively). Theophylline was statistically significantly more effective than placebo ($p=0.013$). **Adverse Events (AE)**

	66% pts reported adverse events. AE per group - F12=66% / F24=64% / Placebo=67% / Theophylline=68% 49% AE were considered mild 12% AE were considered severe There were higher numbers of GI AEs in the theophylline group (whole numbers only given) In the theophylline group, the total number of withdrawals due to AEs was three fold higher than that in the F12 and F24 groups and twofold higher than the placebo group. Pts receiving theophylline were four times more likely to discontinue treatment because of AEs or unsatisfactory therapeutic effect than were pts receiving F24 and three times more likely to discontinue treatment than those receiving F12. There were four deaths. Three occurred in the F12 group and one in the F24 group. Three deaths were considered not related to study medication. One death was due to MI with a rupture of the cardiac septum possibly related to receiving study drug (F12 group).
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	966

Author / Title / Reference / Yr	Rutten-Van, M., Roos, B., & van, N. 1999, "An empirical comparison of the St George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ) in a clinical trial setting", *Thorax* vol. 54, no. 11, pp. 995-1003. Ref ID: 968 (Rutten-van Molken 1999 included in Appleton S, Poole P, Smith B, Veale A, Bara A. Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease patients with poorly reversible airflow limitation (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.).
N=	N=144. Duration=3/12. Geographical Location=Three Dutch outpatient clinics.
Operational Definition	COPD diagnosis as per ATS criteria.
Research Design	RCT. Double blind, double dummy, parallel group design. Random assignment.
Population	Moderate to severe COPD (Asthma excluded).
Intervention	Salmeterol 50ug twice daily plus placebo matched to ipratropium. Salmeterol 50ug + ipratropium 40ug four times daily.
Comparison	Placebo matched to ipratropium plus placebo matched to salmeterol.
Outcomes	QoL
Characteristics	There were no statistically significant differences between the 3 groups in baseline characteristics including QoL Average age 64yrs. Age range 40-75yrs

	Current or previous smokers with history of 10 pack yrs. All maintenance drugs other than the study medication were continued
Results	**Clinical Outcomes:** "Daytime symptom score, morning and evening PEFR, FEV1, specific airway conductance and night time use of rescue drugs showed significantly more improvement in the salmeterol or salmeterol plus ipratropium group than in patients receiving placebo. There were statistically significant additional effects of the combination treatment over and above salmeterol treatment for evening PEFR and FEV1 % predicted". No p values or confidence intervals are presented to support the statistical significance referred to. **Quality of Life:** SGRQ symptom score ($p<0.001$) and the CRQ fatigue ($p<0.05$) and total scores ($p<0.05$) showed statistically significant within-patient improvements in patients receiving salmeterol plus ipratropium. Except for deterioration on the CRQ emotions domain in the salmeterol group, the other domains did not show statistically significant within-patient changes. SGRQ score showed a significantly greater improvement on treatment with salmeterol and ipratropium than on salmeterol alone (mean difference 9.4; 95% CI 2.7-16.1) or placebo (mean difference 8.7; 95%CI 1.3 to 16.2), neither of which showed a significant change. The average differences exceeded the minimally important difference of 4% (established by the designers of the questionnaires). A significantly greater improvement on combination treatment than on salmeterol treatment was also found for the overall CRQ score (mean difference 0.4; 95% CI 0.11-0.69) and the CRQ emotions domain (mean difference 0.51; 95% CI 0.17-0.83). Neither the SGRQ nor the CRQ showed any significant differences between salmeterol and placebo.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	968

Author / Title / Reference / Yr	Sestini P, Renzoni E, Robinson S, Poole P, Ram F.S.F. Short-acting beta$_2$-agonists for stable chronic obstructive pulmonary disease. *The Cochrane Library.Oxford:Update Software* 2003;**Issue 3**.
N=	13 RCTs (all used a cross over design) of at least one wk duration N= 296 (but N=302 in the patient characteristics table)
Population	Adults with stable COPD defined by BTS / ERS / ATS Excludes: Asthma / bronchiolitis / oral rather than inhalation beta$_2$-agonists / acute exacerbations
Intervention	At least 7 days of regular treatment with inhaled short-acting beta$_2$-agonists delivered by metered dose inhaler or nebuliser Drugs include: salbutamol (albuterol), fenoterol, terbutaline, bitolterol, pirbuterol, reproterol and metaproterenol (orciprenaline).

Comparison	Placebo
Outcomes	**Primary outcomes:** Symptom scores including dyspnoea at rest, on exertion, sputum, cough Quality of life Lung function (FEV1, PEFR, FVC, airway resistance) **Secondary outcomes:** Patient preference between drug and placebo Number and type of adverse effects Number of study withdrawals Mortality Exercise capacity Days sick (hospital admission, frequency & severity of exacerbations)
Characteristics	Characteristics table provided within the Cochrane Rv: Female 36/302 (Number of pts in Characteristics table N=302. Trial patients total=296) Age range 32-85 yrs Ex smokers – not known for all the studies Study population varied slightly in terms of baseline severity but most patients had moderate-severe airways obstruction. Respiratory function] All Reversibility] vary Drug] Duration study and washout]
Results	Spirometry End of treatment period FEV1 post bronchodilator spirometry demonstrated a significant difference (WMD=0.140 L/min, 95% CI: 0.04 to 0.25. p=0.008). This was mainly due to studies that used salbutamol and terbutaline. FVC also improved (WMD=0.30 L, 95%CI: 0.02 to 0.58; p=0.03) compared to placebo Peak Flow Rate Unlike spirometry, which is usually measured only at the end of treatment period, PEFR can be recorded daily, usually both in the morning and evening, and therefore represents the overall condition of the patient during the study period, rather than at a single time point. Post-bronchodilator morning PEFR was significantly higher in the treatment group than in the placebo group (WMD=29.2 L/min; 95%CI: 0.3 to 58.1; p=0.05). Post bronchodilator evening PEFR was also significantly higher in the treatment group (WMD=36.8 L/min; 95% CI: 2.6 to 70.9; p=0.04). Breathlessness Four studies reported daily breathlessness scores (Dullinger 1986, Guyatt 1989, Hansen 1990 & Shah 1983) a highly significant

	improvement in daily breathlessness score was observed during treatment with beta$_2$-agonist (SMD=1.33; 95%CI: 1.01-1.65; p<0.00001) Wheeze Not possible to combine data for meta-analysis. Cough Silins 1985 (N=8) data was in a suitable format for inclusion, which did not show any significant difference between treatment and placebo groups. Sputum production Wilson 1980 (N=10) & Silins 1985 (N=8) showed no significant difference in sputum production between the beta$_2$-agonist and placebo groups. Treatment Failures / Exacerbations Five trials reported drop out because of exacerbation. The risk of treatment failure was significantly greater in the placebo group than in the beta$_2$-agonist group (RR=0.49, 95%CI: 0.33-0.73, p<0.00001). Patient preference Four studies presented patient preference. 57% of patients preferred the beta$_2$-agonist compared to 9% for placebo (OR=9.04; 95% CI: 4.64-17.61; p=0.00001). Quality of Life Data for this outcome were not presented in a usable format for inclusion in the review. Guyatt 1989 (N=32) reported highly significant improvements during salbutamol treatment in the scores for the domains for dyspnoea (p=0.003) and fatigue (p=0.0003). Walking Test Combining five studies in a meta-analysis using an SMD, no significant differences were found between the bronchodilator and the placebo groups. Beta$_2$-usage (rescue medication) Only two studies (totalling N=13) presented data in a form suitable for inclusion in a meta-analysis. There was no statistical significance between the two treatment groups. Side effects None of the studies had sufficient numbers or length of observation in order to assess this. Hospital admissions / exacerbation rates / mortality Not reported by the studies.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
NCC CC ID	819
Trials included	Dullinger 1986 (N=10), Guyatt 1988 (N=32), Guyatt 1989 (N=32), Hansen 1990 (N=48), Jaeschke 1991 (N=24), Klock 1975 (N=15), Light 1975 (N=16), Shah 1983 (N=12), Silins 1985 (N=8), Tandon 1990 (N=37), Taylor (N=25), Wilson 1980 (N=10).

Author / Title / Reference / Yr	Shukla, V. K., Husereau, D. R., Boucher, M., Mensinkai, S., Dales, R. (2002). Long-acting beta$_2$-agonists for maintenance therapy of stable chronic obstructive pulmonary disease: A systematic review. Ottawa: *Canadian Coordinating Office for Health Technology Assessment* (CCOHTA). Technology Report no 27.
N=	N= 9 studies; Sample size range= N=29-674 (see included studies for N per independent study) Location=Multiple Sites=Multiple Duration varies between 4 weeks and 12 months follow-up.
Research Design	Prospective, randomized, controlled trials, of both parallel and cross-over designs.
Aim	To critically examine, using best evidence synthesis methodology, the evidence from randomized controlled trials: 1.) Related to the efficacy and safety of long-acting β_2-agonist agents **versus placebo**, with or without the additional use of short-acting β_2-agonist agents, for the maintenance treatment of patients with stable COPD; and 2.) Related to the efficacy and safety of long-acting β_2-agonist agents **versus anticholinergic agents**, with or without the additional use of short-acting β_2-agonist agents, for the maintenance treatment of patients with stable COPD.
Operational Definition	FEV1 of 75% or less than predicted; and FEV1/FVC ratio less than 70% predicted; less than 15% improvement in FEV1 after a dose of a short or a long acting β_2-agonist.
Population	Stable COPD, asthma excluded
Intervention	Long acting β_2-agonist salmeterol or formoterol
Comparison	Placebo or anticholinergic agent
Outcome	Changes in FEV1 Changes in FVC Changes in PEFR Walk test Dyspnoea measurement Additional bronchodilator usage Quality of life COPD exacerbations
Characteristics	No age and gender ratio provided. Non-asthmatic; stable COPD;
Results	**Salmeterol vs Placebo** Compared to placebo, salmeterol significantly increased FEV1 in four studies and formoterol significantly increased FEV1 in two studies. A significant decrease when comparing salmeterol to placebo in additional day-time and night-time rescue bronchodilator

	usage was observed in two studies. No significant improvements in PEFR, distance travelled in a six-minute walk test, transition dyspnoea index (TDI) scores of incidence of exacerbations of COPD were observed with salmeterol versus placebo in any of the studies. **Formoterol vs Placebo** Significant improvements in FVC, PEFR, and patients self-assessed dyspnoea scores were observed with formoterol versus placebo in one study. **Salmeterol vs ipratropium bromide** A study comparing salmeterol and ipratropium bromide did not show any significant changes in FEV1 and TDI scores. **Formoterol vs ipratropium** Formoterol compared to ipratropium did not show significant improvement in any of the outcome measures (shuttle walking test, FEV1, FVC, breathlessness, SGRQ total scores) with the exception of one outcome measure (PEFR) in one study.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ia
Included Studies	Ulrik, 1995, N=66; Newman et al., 1996, N=42; Grove et al., 1996, N=29; Boyd et al. 1997, N=674; Jones and Bosh, 1997, N=283; Mahler et al. 1999, N=145; Rennard et al. 2001, N=179; Rossi et al. 2002, N=418; Stahl et al*. 2002, N=183. *Russian
NCC CC ID	1764

Author / Title / Reference / Yr	Taylor, J., Kotch, A., Rice, K., Ghafouri, M., Kurland, C. L., Fagan, N. A., & Witek, T. J. 2001, "Ipratropium bromide hydrofluoroalkane inhalation aerosol is safe and effective in patients with COPD", *Chest*, vol. 120, no. 4, pp. 1253-1261.Ref ID: 156
N=	N=507 Duration=12wks Location=USA Sites=31 centres
Research Design	Randomised, double blind parallel group placebo controlled.
Aim	To compare the efficacy and safety of ipratropium bromide reformulated with the chlorofluorocarbon (CFC)-free propellant hydrofluoroalkane (HFA)-134a (ipratropium bromide HFA) to that of the marketed ipratropium bromide inhalation aerosol (containing CFC) in pts with COPD.
Operational Definition	"Pt selection followed standard COPD selection criteria" this statement is referenced to ATS 1995. FEV1 <65% predicted normal and FEV1< 70% of the FVC
Population	Moderate to severe COPD (Asthma excluded)
Interventions and Comparisons	Two inhalations, four times daily with one of the following: Ipratropium bromide HFA, 42ug Ipratropium bromide HFA 84ug HFA placebo Ipratropium bromide inhalation aerosol 42ug CFC placebo
Outcomes	Measurements were taken on days 1, 29, 57 and 85 @ 15, 30, 60, 90 and 120 min and hrly thereafter for a total of 8h. FEV1 / FVC / peak change
Characteristics	Concomitant medications – continued use of stable doses of theophylline was allowed during the study (28% pts), regular use of inhaled bronchodilators other than the study drug was not allowed. Temporary increase or additions of theophylline and corticosteroids during exacerbations were permitted but limited to two periods of 5 days. Cromolyn sodium, oral $beta_2$-agonists and beta-blockers were not allowed. Pts were allowed to receive inhaled albuterol for control of symptoms as necessary during the study period. Theophylline was withheld 24hr and beta agonists withheld for 12 hrs prior to PFT. Mean age=66yrs. Range 41 – 87 yrs Sex – 62% males Ethnic origin – Dot detailed Baseline FEV1 L mean 1.06, range 0.20 – 2.46 % Predicted FEV1 mean 40.0, range 10.3 – 77.2

	% FEV1/FVC mean 48, range 22 – 70.0
Results	**Efficacy** Majority of pts (95%) reported that they inhaled the drug four times daily during the 85-day treatment period. The highest dropout rate was observed in the CFC placebo group (23%). Other dropout rates ranged from 6% - 14%. Pts in all active treatment groups had significant bronchodilator responses demonstrated by increases in mean FEV1 from baseline of at least 15%. Bronchodilator response in all active treatment groups was also significantly more than their respective placebo treatments based on FEV1, from 0-6 hrs and peak response. FVC results were similar to those seen with FEV1. There were no significant differences in adverse events among the treatment groups. **Other Efficacy Variables** Adjusted mean physician's global evaluation scores were between 4.8 – 5.4 for all treatment groups representing a rating of "fair to good" . The COPD symptom scores (wheezing, shortness of breath, coughing and tightness of chest) did not change over time and did not differ among the placebo and active treatment groups. Rescue therapy – pts in the placebo groups reported slightly higher use of albuterol. There were no differences in the use of albuterol in the active treatment groups. **Safety** Incidence of adverse events was similar across all treatment groups. Six pts died during the study. None of the six deaths were reported to be related to the study drug.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	156

Author / Title / Reference / Yr	Ulrik, C. S. 1995, "Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: a single centre randomised, double blind, placebo controlled, crossover study. [see comments.]", *Thorax*, vol. 50, no. 7, pp. 750-754. Ref ID: 278
N=	N=66 randomized. Geographical Location=Denmark. Duration= 12 wks 2wk run-in period
Trial Design	Double blind, randomized, crossover comparison trial
Population	COPD Moderate to severe COPD (Baseline FEV1 of 1.0-2.0 l, and <60% of the predicted value, an FEV1/FVC ratio below 60%, and non reversible airways obstruction in a stable phase, defines as an increase in FEV1 of <15% or 300ml 30mins after inhalation of 0.4mg salbutamol). No reversibility of FEV1 after a trial of oral prednisolone 30mg daily for 7 days Entry criteria aged over 40yrs Asthma excluded Treatment with inhaled steroids within the previous 6/12 excluded Inhaled $beta_2$-agonists and anticholinergic drugs were withdrawn. Pts on methylxanthines use continued Short courses of oral corticosteroids were allowed during exacerbations.
Intervention	N=31 Salmeterol 50ug twice daily for 4wks followed by placebo twice daily for 4 wks or vice versa
Comparison	N=32 Placebo / salmeterol
Outcomes	Peak expiratory flow rate (PEF) / Symptom scores and use of rescue $beta_2$-agonist / Subjective pts evaluation
Characteristics	M/F 33/30 Mean age 65yrs. Current smokers. Mean number of pack yrs smoked was 44. Rescue therapy salbutamol Diskhaler 0.4mg during treatment periods

Results	**One person performed all evaluations.** PEF *Morning PEF* The mean morning PEF during the salmeterol period was 238 (SD 10) l/min and the corresponding valued during the placebo period was 226 (10) l/min. Mean treatment difference was 12 l/min (95% CI: 6 to 17; p<0.001) ***Evening PEF*** There was no difference in mean evening PEF values FEV1 and FVC Between the two treatment periods no differences were found in: Mean baseline FEV1, FVC and FEV1/FVC Mean reversibility in FEV1 or mean FEV1/FVC, and FEV1/FVC after administration of salbutamol Symptom Score Daytime and nighttime median symptom scores were significantly lower during the salmeterol period than during the placebo period (p<0.001). Rescue Medication Compared with placebo treatment with salmeterol was associated with significantly less use of rescue salbutamol both during the day and the night (p=0.02 and p<0.001 respectively). Subjective Assessment The salmeterol period was rated significantly higher than the placebo period (p=0.01) ***Side Effects*** Side effects only discussed in terms of being similar between the two treatment periods, no statistical data is provided, possibly due to the small numbers involved. 53 of the 63 pts did not report any side effects.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	278

Author / Title / Reference / Yr	van Noord, J. A., Bantje, T. A., Eland, M. E., Korducki, L., & Cornelissen, P. J. G. 2000, "A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease", *Thorax*, vol. 55, no. 4, pp. 289-294. Ref ID: 169
N=	N=288. Duration=13wks. Location=Netherlands. Sites=14
Research Design	Double blind, double dummy, parallel group study

Aim	To evaluate and compare the efficacy and safety of tiotropium and ipratropium during long-term treatment. Study reports the first 13 wks of a 1yr study.
Operational Definition	COPD according to ATS criteria. FEV1 <65% predicted and a ratio of FEV1 to FVC of <70%.
Population	COPD (Asthma excluded). Includes exacerbations.
Interventions & Comparisons	Tiotropium 18ug once daily from a dry powder inhaler + ipratropium matched placebo four times daily
	Ipratropium 40ug four times daily from a MDI + tiotropium matched placebo once daily.
Outcomes	Times Measures taken on days 1, 8, 50 and 92 @ 0.5,1,2,3,4,5,6hrs Outcomes Lung function / PEF / concomitant salbutamol use
Characteristics	Pts continued to take methylxanthines, inhaled steroids, oral steroids up to 10mg prednisone per day and mucolytics. LABA (inhaled), oral $beta_2$-agonists, and cromolyn sodium were not allowed for 1/12 before & throughout the study. Anticholinergics were allowed during run in but were discontinued at randomisation. Used open label salbutamol as rescue medication as necessary. Mean age=64yrs Sex=83% Male Ethnic origin=Not detailed.
Results	Tiotropium achieved a significantly greater improvement than ipratropium ($p<0.05$) in trough, average and peak FEV1 and in trough and average FVC levels. On all test days tiotropium produced a greater improvement in FEV1 than ipratropium starting 3h after inhalation ($p<0.05$). Morning and evening PEF was better in the tiotropium group, the difference in morning PEF being significant up to 10wks and the evening PEF up through week 7 of treatment ($p<0.05$). The use of concomitant salbutamol was lower in the tiotropium group ($p<0.05$). There were no group differences for adverse events.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	169

Author / Title / Reference / Yr	van Noord, J. A., de Munck, D. R. A. J., Bantje, T. A., Hop, W. C. J., Akveld, M. L. M., & Bommer, A. L. 2000, "Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium", *European Respiratory Journal*, vol. 15, no. 5, pp. 878-885. Ref ID: 175
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	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 ≤65% 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 7 days during run-in period **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.
Intervention	Salmeterol 50ug plus ipratropium bromide 40ug (combination) q.i.d. (n = 47) *(Patients on stable dose of inhaled corticosteroids could continue treatment. salbutamol given as rescue medication)*
Comparison	1) Salmeterol 50ug plus ipratropium bromide matched placebo (salmeterol alone) b.i.d. (n = 47) 2) Salmeterol-matched placebo plus ipratropium bromide- matched placebo (placebo) b.i.d. (n = 50) *(Patients on stable dose of inhaled corticosteroids could continue treatment. salbutamol given as rescue medication)*
Outcome	Lung function measured for 12 h after 1st 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

	Salmeterol plus ipratropium	Salmeterol	Placebo
Sex M/F %	88/12	89/11	86/14
Age yrs	63 ± 7	65 ± 6	63 ± 7
FEV1 L	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.3
FEV1 %pred	41 ± 12	42 ± 10	38 ± 10
FVC L	3 ± 8	2.8 ± 0.8	2.8 ± 0.7
FEV1/FVC %	42 ± 9	43 ± 8	41 ± 9
Raw kPa/L/s	0.65 ± 0.23	0.63 ± 0.23	0.72 ± 0.3
sGaw kPa/L/s	0.33 ± 0.13	0.35 ± 0.18	0.29 ± 0.09

No significant differences at baseline. Medication usage comparable among groups.

Results

12 week treatment

Symptom scores (day and night time)

Throughout treatment

Placebo group – decrease from 1.9 ± 0.1 to 1.7 ± 0.1 (NS)

Salmeterol group – decrease from 2.0 ± 0.1 to 1.4 ± 0.1 ($p<0.001$)

Combination group – decrease from 2 ± 0.1 to 1.3 ± 0.1 ($p<0.001$)

Significant difference between change in daytime symptoms score between both salmeterol alone ($p<0.005$) and salmeterol + ipratropium ($p<0.001$) compared with placebo.

No significant difference was seen between salmeterol and combination groups.

Days with minimal symptoms (score <1)

Combination therapy (run-in 14 ± 3.0% vs treatment 57 ± 3.0) ($p<0.05$)

Salmeterol alone (run-in 14 ± 2.9% vs treatment 49 ± 3.0) ($p<0.05$)

Placebo group (run-in 17 ± 3.7% vs treatment 34 ± 4.0) ($p<0.05$)

Improvements in the combination group and salmeterol group were significantly better than in the placebo group ($p<0.05$)

Night time symptom scores

No differences were observed between the three groups throughout treatment

Rescue medication

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 ($p<0.01$).

No significant difference was observed between the two active treatments.

	Days with additional use of salbutamol Combination therapy (run-in 93 ± 3.2% vs treatment 27 ± 5.5) Salmeterol group (run-in 97 ± 2.2% vs treatment 34 ± 5.5) Placebo group (run-in 98 ± 1.8% vs treatment 74 ± 5.0) Nights with additional use of salbutamol Combination therapy (run-in 50 ± 6.9% vs treatment 24 ± 4.1) Salmeterol group (run-in 37 ± 6.3% vs treatment 17 ± 2.9) Placebo group (run-in 37 ± 6.1% vs treatment 33 ± 6.3) **Peak expiratory flow** Improvements in morning PEFs were significantly better in both active treatment groups than in the placebo group ($p<0.001$). No difference was observed between the salmeterol and combination treatment groups Morning PEF (L/min) Combination therapy (run-in 252 ± 11 vs treatment 277 ± 23) ($p<0.001$ compared with placebo) Salmeterol group (run-in 246 ± 9 vs treatment 262 ± 11) ($p<0.001$ compared with placebo) Placebo group (run-in 238 ± 9 vs treatment 236 ± 9) Evening PEF Combination therapy (run-in 271 ± 11 vs treatment 297 ± 11) ($p<0.01$ compared with salmeterol alone) Salmeterol group (run-in 257 ± 10 vs treatment 271 ± 11) Placebo group (run-in 259 ± 10 vs treatment 253 ± 10) **FEV1** During 12 week treatment Combination treatment – % increase 8 ± 0.8% pred ($p<0.01$ vs salmeterol alone and vs placebo) Salmeterol group - % increase 5 ± 0.9% pred ($p<0.01$ vs placebo) Placebo group - % increase 1 ± 0.9% pred **FVC** During 12 week treatment Combination treatment – % increase 12 ± 1.2% pred ($p<0.01$ vs salmeterol alone and vs placebo) Salmeterol group - % increase 7 ± 1.2% pred (NS vs placebo) Placebo group - % increase 4 ± 1.2% pred **sGaw** Combination treatment – % decrease 61 ± 6% pred ($p<0.01$ vs salmeterol alone and vs placebo) Salmeterol group - % decrease 36 ± 6% ($p<0.01$ vs placebo) Placebo group - % decrease 16 ± 6% from baseline **Adverse events**

	No significant difference between groups. Most common adverse events were headache and cough. 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) **Conclusion** 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.
SIGN Quality Rating	+ (Blinded double critical appraisal)
Hierarchy of Evidence Grading	1b
NCC CC ID	175

Author / Title / Reference / Yr	Vincken, W., van Noord, J. A., Greefhorst, A. P. M., Bantje, T. A., Kesten, S., Korducki, L., & Cornelissen, P. J. G. 2002, "Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium", *European Respiratory Journal*, vol. 19, no. 2, pp. 209-216. Ref ID: 33
N=	N=535 Duration=1 yr Geographical Location=29 sites in Netherlands and Belgium
Research Design	Two one yr studies incorporating a randomised double blind, double dummy parallel group design. Pts from the Van Noord et al 2000 trial continued into a 1yr RCT and the current study by Vincken et al 2002 describes the combined results of the Van Noord trial and a second large multi centre 1 yr trial.
Aim	Health outcome evaluation over a 1 yr period
Operational Definition	FEV1 <65% of the predicted normal value and <70% of FVC
Population	COPD (Asthma excluded)
Intervention	Tiotropium 18ug once daily dry powder capsule inhaled via a pharmaceutical company device
Comparison	Ipratropium 40ug q.i.d. via a MDI
Outcomes	Spirometric results, PEFR, salbutamol use and effects on dyspnoea, HRQoL, exacerbations
Characteristics	Short and long acting $beta_2$-agonists and inhaled anticholinergic medications were not permitted. Concomitant use of theophyllines & inhaled steroids were allowed. Salbutamol MDI 100ug as needed for acute symptom relief.

	Mean age=64yrs Sex=85% Male Ethnic origin=Not detailed
Results	**Spirometry** Tiotropium was superior to ipratropium ($p<0.05$) at all time points on all test days except for the first 2h following the first dose and up to 1h after the dose 1 wk later. At the end of 1 yr, trough FEV1 was 120 ml above day 1 baseline for pts receiving tiotropium, and had declined by 30ml for those receiving ipratropium (difference of 150ml between groups, $p<0.001$ at all time points). FVC paralleled the FEV1 results. Spirometry results were consistent across centres. **PEFR** Throughout the 1 yr treatment, morning and evening PEFR improved significantly more in the tiotropium group than in the ipratropium group ($p<0.01$ at all wkly intervals). **Dyspnoea** Tiotropium significantly improved all three components of the TDI, as well as the focal score, on all test days compared to ipratropium ($p<0.05$). **Use of as needed (rescue) salbutamol** On average, pts receiving tiotropium self-administered approx four fewer inhalations of salbutamol/wk^{-1} compared to pts receiving ipratropium ($p<0.05$ for 40 to 52 wks). **Health Related Quality of Life** Over the 1 yr treatment period, the SGRQ total score decreased (improved) in both groups, but gradually returned towards baseline in the ipratropium group. Improvements were maintained over the yr in the tiotropium group, and were superior to ipratropium ($p<0.05$). **Exacerbations** Tiotropium reduced the number of exacerbations (by 24%, $p<0.01$), and increased time to first exacerbation ($p<0.01$) and time to first hospitalisation for a CIOD exacerbation ($p<0.05$) compared with ipratropium. **Adverse Events** Apart from an increased incidence of dry mouth in the tiotropium group, adverse events were similar between treatments.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	33