Supplementary material

Table S1. Large randomised controlled treatment trials reported after 2007. This table complements the NICE 2010 guidelines evidence tables [16] and summarises selected key studies including those discussed in this article.

Author	Duration	Key outcomes
Do ICS, bronchodilators or combinations of these reduce the rate of FEV_1 decline?		
Celli, 2008 (n=6,112)	3 years	In patients with moderate-to-severe COPD salmeterol plus fluticasone propionate, or either component alone, reduced the rate of decline of FEV_1
Jenkins, 2009 (n=6,112)	3 years	Salmeterol plus fluticasone propionate reduced moderate-to-severe exacerbations and improved status and FEV_1 across GOLD stages (GOLD stage II to Stage IV)
Tashkin, 2008b (n=5992)	4 years	In COPD patients (FEV_1 ≤70%) tiotropium therapy was associated with improvements in lung function, quality of life, and exacerbations but did not significantly reduce the rate of decline in FEV_1. During the trial patients could use any respiratory medications except other inhaled anticholinergic drugs.
Can a long-acting inhaled bronchodilator modify endpoints not usually associated with bronchodilation?		
Bogdan, 2011 (n=613)	12 weeks	Formoterol (4.5 µg and 9 µg twice daily) administered to Japanese and European patients with moderate-to-severe COPD significantly increased FEV_1 60-min post-dose compared with placebo ($p < 0.001$ for both). The higher formoterol dose reduced the need for reliever medication and improved health-related quality-of-life compared with the lower dose.
Tashkin, 2010a (n=5992)	4 years	A subgroup analysis by smoking status showed that tiotropium (compared with placebo), had no association with lung function decline but was associated with improvements in pre- and post-bronchodilator lung function, reductions in the risk and frequency of exacerbations across all smoking categories and improvements in health-related quality of life in smokers and ex-smokers with COPD (FEV_1 ≤70%).

Tashkin, 2010b (n=5992)	4 years	A subgroup analysis by gender showed men and women with COPD (FEV_1 ≤70%) treated with tiotropium had similar benefits with improvement in FEV_1 and FVC, HRQL and exacerbations of COPD.
Do combinations of ICS with long-acting bronchodilators provide better clinical outcomes than bronchodilator alone?		
Wedzicha, 2008 (n=1,323)	2 years	No difference in exacerbation rate between salmeterol plus fluticasone propionate and tiotropium. A small statistically significant beneficial effect found for health status for patients on salmeterol plus fluticasone propionate versus tiotropium, and fewer deaths in salmeterol plus fluticasone propionate-treated patients compared with tiotropium-treated patients.
Tashkin, 2008a (n=1704)	6 months	Evaluated the efficacy and tolerability of budesonide/formoterol administered via one hydrofluoroalkane pMDI in patients with COPD. Budesonide/formoterol pMDI demonstrated significantly greater efficacy for pulmonary function on both co-primary endpoints versus the pre-specified comparators (formoterol and budesonide). Dyspnoea scores and HRQL were significantly improved with budesonide/formoterol versus both single components and placebo.
Anzueto, 2009 (n=797)	52 weeks	COPD patients with moderate-to-severe exacerbations were randomised to fluticasone propionate plus salmeterol or salmeterol twice-daily. Statistically significant reductions in albuterol use, dyspnoea scores, and night-time awakenings were reported together with benefits on quality of life were seen with fluticasone propionate plus salmeterol compared with salmeterol.
Rennard, 2009 (n=1964)	12 months	Budesonide/formoterol (pMDI) improved pulmonary function and reduced symptoms and exacerbations over 1 year in patients with moderate to very severe COPD.
Calverley, 2010b (n=718)	48 weeks	In patients with severe, stable COPD, beclomethasone/formoterol treatment improved pulmonary function and reduced symptoms compared to formoterol. The overall rate of COPD exacerbations/patient/year was similar and not statistically significantly different among treatments (beclomethasone/formoterol, budesonide/formoterol,

		and formoterol).
Doherty, 2012 (n=1196)	52 weeks	Patients with moderate-to-very severe COPD were assigned to twice-daily inhaled mometasone furoate either alone or in combination with formoterol fumarate, or placebo. The combination improved lung function and respiratory health status, and reduced exacerbations more than either monocomponent.
Tashkin, 2012a (n=1055)	52 weeks	Patients with moderate-to-very severe COPD were randomised to mometasone furoate plus formoterol fumarate or a single component or placebo. Mometasone furoate plus formoterol fumarate twice daily was effective based on improvements in lung function and quality of life as well as a reduction in exacerbations.
Tashkin, 2012b (n=2251)	52 weeks	Patients treated with mometasone furoate plus formoterol demonstrated significant improvements in lung function, health status, and exacerbation rates. A trend showing a dose-response effect was observed in the lung function measurements.
Sharafkhaneh, 2012 (n=1219)	12 month	In COPD patients with an exacerbation history, budesonide/formoterol (320/9 µg and 160/9 µg) reduced exacerbation rates (number per patient-treatment year) by 34.6% and 25.9%, respectively, versus formoterol ($p \leq 0.002$).
Kardos, 2007 (n=994)	44 weeks	Combination therapy with salmeterol/fluticasone propionate resulted in 35% decrease in the annualised rate of moderate and severe COPD exacerbations compared with salmeterol alone. The combination also increased time to first exacerbation significantly more than salmeterol alone ($p < 0.0001$).
Does combining a LAMA with a LABA improve lung function and other outcomes?		
Rabe, 2008 (n=605)	6 weeks	In COPD patients with moderate COPD (GOLD stages II and III) tiotropium plus formoterol was reported as superior in daytime lung function outcomes compared with salmeterol plus fluticasone.
Vogelmeier, 2008 (n=847)	24 weeks	Examined the clinical efficacy and safety of formoterol, tiotropium and the combination in patients with COPD. The three active treatments were significantly more effective than placebo for COPD-related 'bad days', symptoms, use of rescue medication and peak expiratory flow, and aspects of health-related quality of life. COPD-

		related adverse events were more common with tiotropium.
Mahler, 2012 (n=1134 and n=1142)	12 weeks	In 2 identical studies patients with moderate to severe COPD (concurrently receiving open-label tiotropium once daily) received either indacaterol once daily or matching placebo. Compared with tiotropium monotherapy, indacaterol plus tiotropium provided greater bronchodilation and lung deflation (with increased resting inspiratory capacity).
Wedzicha, 2013 (n=2224)	64 weeks	In COPD patients (GOLD stage III-IV) dual bronchodilator (indacaterol plus glycopyrronium) was reported as superior in preventing moderate to severe COPD exacerbations compared with the glycopyrronium alone. Improvements in lung function and health status were also reported.
Bateman, 2013 (n=2144)	26 weeks	QVA149, a once-daily, dual bronchodilator (fixed dose indacaterol with glycopyrronium) was compared with the single components or placebo in patients with moderate-to-severe COPD. Dual bronchodilation had superiority, with clinically meaningful outcomes versus placebo, and superiority versus treatment with a single bronchodilator. Safety and tolerability profile reported as similar to placebo.
Vogelmeier, 2013 (n=7384)	1 year	Compared to salmeterol, tiotropium significantly increased time to first exacerbation in GOLD stage II (n=3614) and maintenance therapy naïve (n=1343) patient subgroups, and the annual rate of exacerbations in the maintenance naive subgroup.
Does triple therapy combining an ICS, LABA and LAMA provide additional clinical benefits?		
Welte, 2009 (n=660)	12 weeks	In COPD patients (prebronchodilator FEV_1 ≤50% predicted normal value), budesonide plus formoterol added to tiotropium in comparison to tiotropium alone improved overall lung function and day/night-time symptoms and reduced severe exacerbations.
Are once-daily treatment regimens preferable to twice-daily?		
Calverley, 2008 (n=911)	52 weeks	Once-daily mometasone furoate (administered via a DPI) improved lung function and health status in subjects with moderate-to-severe COPD and was comparable to twice daily mometasone furoate.

Niewoehner, 2009 (n=676)	84 days	Patients with moderate to very severe stable COPD (mean FEV_1=39% of predicted). Patients previously maintained on an ipratropium/albuterol combination taken four times daily were successfully switched to tiotropium once daily.
Bateman, 2010b (n=1990)	1 year	Tiotropium administered once daily via the Respimat® Soft Mist™ Inhaler in COPD patients (mean FEV_1: 1.09L). Compared with placebo the exacerbation rate was significantly lower with tiotropium, versus placebo, and the health-related quality of life and Mahler Transition Dyspnoea Index were significantly improved.
Vogelmeier, 2011 (n=7376)	1 year	Compared the effect of treatment with tiotropium, once daily, with salmeterol twice daily, on the incidence of moderate or severe exacerbations in patients with moderate-to-very-severe COPD and a history of exacerbations in the preceding year. Tiotropium was better than salmeterol in preventing exacerbations.
Korn, 2011 (n=1123)	12 weeks	Compared indacaterol once-daily with salmeterol twice-daily in patients with moderate-to-severe COPD and showed indacaterol had statistically superior bronchodilation over salmeterol (sustained for 24 hours post-dose). Compared with salmeterol, indacaterol reduced breathlessness and the use of rescue medication.
Kornmann, 2011 (n=1002)	6 months	Patients with moderate-to-severe COPD were randomised to indacaterol (150 mg once daily), salmeterol (50 mg twice daily) or placebo. Indacaterol-treated patients had a significant and clinically relevant bronchodilator effect over 24 hours post-dose and had improved health status and dyspnoea compared with salmeterol. Trough FEV_1 was significantly higher with indacaterol than with salmeterol.
Arievich, 2012 (n=385)	28 days	Compared the efficacy and safety of once or twice-daily glycopyrronium bromide regimens in patients with moderate-to-severe COPD. Glycopyrronium bromide once daily provided significant bronchodilation over 24 hours, and FEV_1 $AUC_{0\text{-}24h}$ was not significantly different than the same total daily dose administered twice daily.
Kerwin, 2012a (n=1066)	52 weeks	Patients with moderate-to-severe COPD randomised to NVA237 (glycopyrronium bromide), placebo or open-label tiotropium. NVA237 significantly improved lung function, dyspnoea, health status, exacerbations and rescue medication use, compared with placebo, and was comparable to tiotropium.

Dahl, 2010 (n=1732)	52 weeks	In patients with moderate to severe COPD, indacaterol 300 mg or 600 mg administered once-daily, increased 24 hour post-dose FEV_1, and improved transition dyspnoea score more than formoterol administered twice daily.
Do muscarinic antagonists have inherent adverse effects on the cardiovascular system?		
Tashkin, 2010b (n=5992)	4 years	A subgroup analysis by gender showed that for all cardiac adverse events, tiotropium (compared with placebo) was not associated with an increased risk in either men or in women with COPD (FEV_1 ≤70%).
Jones, 2012 (n=828)	24 weeks	Two doses of aclidinium bromide (200 or 400µg twice daily) were evaluated in patients with moderate to severe COPD. The incidence of anticholinergic adverse events was reported as low, and similar to placebo. In comparison with placebo, aclidinium bromide significantly improved bronchodilation, health status and dyspnoea.
Worth, 2011 (n=4365)		Patients with moderate-to severe COPD treated with either indacaterol, formoterol, salmeterol, tiotropium or placebo for ≥6 months. Tiotropium, compared with placebo, was associated with an increased risk for cardiovascular and cerebrovascular AEs.
Kerwin, 2012b (n=561)	12 weeks	Twice-daily aclidinium (200 and 400 µg) was compared with placebo in patients with moderate-to-severe COPD. Both doses of aclidinium were associated with significant improvements in bronchodilation, health status, and COPD symptoms. Incidence of adverse event was similar across the 3 treatment groups.
Wise, 2013 (n=17,135)	Mean follow-up 2.3 years	Tiotropium Respimat at a dose of 5 µg or 2.5 µg had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 µg in these patients with COPD. Causes of death and incidences of major cardiovascular adverse events were similar in the three treatment groups.
Do ICS increase the risk of pneumonia?		
Crim, 2009 (n=6,112)	3 years	After adjusting for time on treatment, the reported rate of pneumonia was higher in the fluticasone propionate and salmeterol/fluticasone propionate treatment arms compared with salmeterol or placebo. Risk factors for pneumonia were identified as age ≥55 years, FEV_1 <50% predicted, COPD exacerbations in year prior to the study, worse Medical Research Council dyspnoea scores and body mass index <25 kg/m^2.

Fergusson, 2008 (n=782)	12 months	COPD patients (FEV_1 ≤50% of predicted normal) were randomised to either fluticasone propionate plus salmeterol or salmeterol twice daily. Fluticasone propionate plus salmeterol was more effective at reducing the rate of moderate to severe exacerbations, however a higher reporting of pneumonia was observed.
Calverley, 2011 (n=1,323)	2 years	In COPD patients, pneumonia occurred more often after a treated, or untreated unresolved exacerbation in those receiving salmeterol plus fluticasone propionate (n=32) than in those receiving tiotropium (n=7).
Could antibiotics be used differently/more effectively in COPD?		
Sethi, 2010 (n=1157)	48 weeks	Intermittent prophylactic therapy with moxifloxacin was effective in preventing acute exacerbations in COPD patients with purulent/mucopurulent sputum at baseline. The reduction was seen in COPD of all severity categories, smokers and ex-smokers, and in patients receiving concomitant COPD treatments including inhaled steroids and long-acting bronchodilators.
Albert, 2011 (n=1142)	1 year	In COPD patients (FEV_1 <70%), daily azithromycin (versus placebo) alongside usual treatment, decreased the frequency of exacerbations and improved quality of life. Audiogram-confirmed hearing decrements occurred in some patients (25% versus 20%, respectively).
Wilson, 2012 (n=1372)	8 weeks	Moxifloxacin was as effective as amoxicillin/clavulanic acid in the treatment of outpatients with acute exacerbations of COPD (with Anthonisen type 1 exacerbations of moderate-to-severe COPD.
Rabe, 2013 (n=7376)	1 year	Assessment of the seasonal pattern of moderate and severe exacerbations in COPD patients (randomised to either tiotropium or salmeterol) reported an increase of bacterially induced exacerbations treated with antibiotics during October to March without a clear indication for their need. Further investigation of the factors influencing antibiotic prescribing are required.
Do PDE-4 inhibitors improve clinical outcomes?		
Calverley, 2007b (n=1514)	1 year	In severe (GOLD stage III and IV), stable COPD, roflumilast (PDE-4 inhibitor) produced a modest but significant improvement in lung function without changing exacerbation rate or health status. Less exacerbations were

		reported in GOLD stage IV patients during roflumilast treatment.
Fabbri, 2009 (n=935)	24 weeks	Patients with moderate-to-severe COPD were assigned to oral roflumilast or placebo once a day (in addition to salmeterol [M2-127 study]). Compared with placebo, roflumilast improved mean prebronchodilator FEV_1 and benefitted other lung function measurements.
Fabbri, 2009 (n=744)	24 weeks	Patients with moderate-to-severe COPD were assigned to oral roflumilast or placebo once a day (in addition to tiotropium [M2-128 study]). Compared with placebo, roflumilast improved mean prebronchodilator FEV_1 and benefitted other lung function measurements.
Calverley, 2009 (n=3091)	52 weeks	Two identically designed placebo-controlled, double-blind, multicentre trials conducted in two different COPD populations. Patients were randomly assigned to oral roflumilast (500 µg once per day). FEV_1 increased by 48 mL with roflumilast compared with placebo ($p<0.0001$). The rate of exacerbations that were moderate or severe per patient per year was 1.14 with roflumilast and 1.37 with placebo (reduction 17% [95% CI 8-25], $p<0.0003$).
Does carbocysteine reduce the rate of exacerbations in COPD?		
Zheng, 2008 (n=709)	1 year	In Chinese patients with COPD, the numbers of exacerbations per patient per year declined significantly in the carbocysteine group versus the placebo group.

AE: adverse event; AUC: area under the curve; COPD: chronic obstructive pulmonary disease; DPI: dry powder inhaler; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global initiative for chronic Obstructive Lung Disease; HRQL: health-related quality of life; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; NICE: National Institute for Health and Care Excellence; pMDI: pressurised metered-dose inhaler.

Table S2. Large observational studies reported after 2007. This table complements the NICE 2010 guidelines evidence tables [16] and summarises selected key studies including those discussed in this article.

Author (number of participants)	Duration	Key outcomes
Does severity of airflow restriction correlate with other variables such as dyspnoea, health status, etc?		
Agusti, 2010 (n=2746)	3 years	Cross-sectional analysis of the baseline data from ECLIPSE. The severity of airflow limitation in COPD patients was poorly related to the degree of breathlessness, health status, presence of co-morbidity, exercise capacity and number of exacerbations reported in the year before the study with a concurrent wide distribution within each GOLD stage.
Does smoking cessation influence risk of exacerbations?		
Au, *et al*, 2009 (n=23,971)	Median follow-up 3.87 years	A cohort study which assessed current smoking status and duration of smoking abstinence by self-report in current and past smoking veterans. Compared to current smokers, former smokers were at a significantly decreased risk of COPD exacerbation. Smoking cessation was associated with, and the reduction was dependent upon, the duration of abstinence.
Is early initiation of ICS a cost-effective intervention?		
Akazawa, 2008 (n=10,271)	≤24 months after initiating bronchodilator treatment	An individual-level, fixed-effects model was used to estimate the unbiased effects of adding ICS treatment on monthly medical expenses and likelihood of severe exacerbations among COPD patients, initially treated with regular bronchodilators. ICS treatment reduced exacerbations, with an initial increase in total costs for the full sample. Compared with younger COPD patients, those aged ≥50 had reduced costs and improved outcomes.
Dal Negro, 2011	6 years	Observational study investigating the effectiveness in primary care of LABA and ICS fixed

(n=1,125)		combinations for treating COPD. Since the official recommendation, both morbidity of COPD and the consumption of healthcare resources have decreased.
Is bronchodilator reversibility a useful phenotypic characteristic?		
Albert, 2012 (n=1,831)	3 years	ECLIPSE cohort. Post-salbutamol FEV_1 change was similar in COPD patients and smoking controls but was influenced by baseline lung function and the presence of emphysema. Bronchodilator reversibility status varied temporally and did not distinguish clinically relevant outcomes and was an unreliable phenotype.
Do different ICS/LABA combinations impact risk of exacerbations differently?		
Blais *et al*, 2010 (n=2,262)	1 year	Population-based, matched cohort study conducted using administrative Canadian health care databases. COPD patients treated with budesonide/formoterol were less likely to have emergency department visits and hospitalisations for COPD and used fewer doses of anticholinergic medication than patients treated with fluticasone propionate/salmeterol in the year after treatment initiation.
Suh, 2010 (n=2,923)	12 months	Retrospective cohort analysis. Bronchodilators, with or without ICS, in COPD patients resulted in a lower exacerbation rate when compared with inhaled corticosteroid monotherapy.
Roberts, 2011 (n=6,770)	6 months	A retrospective cohort study assessed COPD-related outcomes including exacerbation events. For most outcomes of interest, budesonide/formoterol fumarate dihydrate and fluticasone propionate/salmeterol showed comparable real-world effectiveness. No significant differences in total COPD-related medical costs in the 6-month period after initiation of combination therapy.
Chatterjee, 2012 (n=3,333)	Follow-up period to a maximum of 1 year	Retrospective cohort study compared the risks of exacerbations and COPD-related healthcare costs between COPD patients initiating tiotropium alone and or fluticasone-salmeterol added to tiotropium. Combination therapy compared with monotherapy was associated with significant reductions in the adjusted risks of moderate exacerbation and any exacerbation over the follow-up

		period at almost equal cost.
Larsson, 2013 (n=5,468)	10 years. Follow up period to a maximum of 11 years	Matched-cohort, register-linkage study of COPD patients. COPD exacerbation rates were 26.6% lower among patients treated with budesonide/formoterol than with fluticasone/salmeterol (p< 0.0001). Yearly rates for COPD-related hospitalisations were 29.1% lower with budesonide/formoterol than with fluticasone/salmeterol (p < 0.0001).
Do different ICS/LABA combinations carry different risks of pneumonia?		
Mapel, 2010 (n=5,245)		Retrospective, longitudinal, nested case-control. Treatment with ICS or an ICS/LABA combination inhaler was not associated with a significantly increased risk of developing pneumonia.
Janson, 2013 (n=5468)	10 years	Matched-cohort, register-linkage study of COPD patients. Rates of pneumonia and admission to hospital were higher in patients treated with fluticasone/salmeterol compared with budesonide/formoterol: rate ratio 1.73 (95% CI 1.57–1.90; p<0.001) and 1.74 (1.56–1.94; p<0.001), respectively. Mortality related to pneumonia was higher in the fluticasone/salmeterol group than in the budesonide/formoterol group with a hazard ratio of 1.76 (1.22–2.53; p=0.003).
Do ICS influence outcomes in COPD patients with pneumonia?		
Ernst, 2007 (175,906)	Duration of follow-up 7.1 (±4.04) year	A nested case-control study within a cohort of Canadian patients with COPD (aged ≥66 years). In all 23,942 COPD patients were hospitalised for pneumonia during follow-up. The use of ICS was associated with an excess risk of pneumonia hospitalisation, and pneumonia hospitalisation followed by death within 30 days in elderly patients with COPD.
Joo, 2010 (n=145,586)	Average duration of follow-up 1.49 (SD=1.11) years	A nested case-control study using data from the Department of Veterans Affairs and Centers for Medicare and Medicaid Services showed the use of ICS in patients with newly diagnosed COPD was associated with an increased risk of hospitalisation for pneumonia.

	per person	
Chen, 2011 (n=15,768)		A retrospective cohort study examining the effects of prior use of ICS on clinical outcomes for patients with COPD hospitalised with pneumonia. In these patients, prior outpatient therapy with ICS was associated with significantly lower 30- and 90-day mortality, and decreased use of mechanical ventilation.
Thornton Snider, 2012 (n=50,545)		A nested case control analysis studied the relationship between ICS use and pneumonia risk in a cohort of COPD patients. Using any ICS during the past year was associated with increased risk of a pneumonia episode. Compared to non-users, pneumonia risk was highest for current users and current high-dose ICS users.
Suissa, 2013 (n=163,514)	5.4 years	In a new-user cohort of COPD patients, ICS use increased serious pneumonia risk, particularly with fluticasone. The elevated risk of serious pneumonia was sustained with long-term use but declined after discontinuation and disappeared after 6 months.
Do theophyllines influence rates of exacerbation?		
Cyr, 2008 (n=36,492)		Population-based cohort study to determine the effectiveness of theophyllines on moderate to severe COPD exacerbations in users of oral theophyllines, ICS and long acting inhaled β_2-agonists. Theophylline use was associated with a reduced rate of COPD exacerbations among all COPD patients, but was less effective than inhaled corticosteroids for those with frequent exacerbations.
Lee, 2009a (n=183,573)		Retrospective cohort study. Patients receiving regimens that included theophylline had slightly increased risks of mortality, COPD exacerbations, and COPD hospitalisations compared with patients receiving the same regimens without theophylline.
Does early introduction of ICS/LABA have advantages over tiotropium as maintenance therapy		
Dalal, 2009		Retrospective, observational, cohort study. Initiation of maintenance therapy with fluticasone

(n=14,689)		propionate/salmeterol was associated with significant reduction in total costs (medical and pharmacy) relative to costs associated with ipratropium bromide/albuterol or ipratropium bromide and tiotropium bromide.
Lee, 2009b (n=42,090)	Up to 547 days	Cohort study. Regimens that included tiotropium + ICS + LABA in combination were associated with reduced risk of all-cause mortality, COPD exacerbations, and COPD hospitalisations compared with ICS + LABA. The 3 regimens that included tiotropium and the 4 combination regimens that included tiotropium + ICS + LABA + ipratropium were associated with increased mortality risk.
Dalal, 2011a (n=14,305)	12 months	Retrospective, observational cohort study. Initiation of maintenance therapy with fluticasone/salmeterol xinafoate, compared with tiotropium was associated with significant reductions in risk of severe exacerbations, health care utilisation, and COPD-related medical and total costs.
Dalal, 2011b (n=43,792)	12 months of follow-up	Retrospective, cohort study. Initiating treatment with fluticasone-propionate/salmeterol was associated with significantly better clinical and economic outcomes compared with short- and long-acting anticholinergic therapy. Mean number of COPD-related hospitalisations, emergency department visits, and outpatient visits associated with an oral corticosteroid or antibiotic were lower for fluticasone-propionate/salmeterol than ipratropium and tiotropium.
Dalal, 2012a (n=4001)	1 year of follow-up	Retrospective, study in COPD patients with co-morbid depression/anxiety. Fluticasone propionate/salmeterol compared with anticholinergics was associated with more favourable COPD-related outcomes and lower COPD-related utilisation and medical costs.
Dalal, 2012b (n=1936)	12 months	Retrospective study. Patients receiving fluticasone propionate/salmeterol as maintenance therapy following an initial COPD-related hospitalisation or emergency department visit experienced better clinical and economic outcomes than patients receiving an anticholinergic (tiotropium or

		ipratropium with or without albuterol).

COPD: chronic obstructive pulmonary disease; ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FEV_1: forced expiratory volume in 1 second; GOLD: Global initiative for chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; NICE: National Institute for Health and Care Excellence.