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[Intervention Review]

Inhaled corticosteroids for stable chronic obstructive pulmonary disease

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ABSTRACT

Background

The role of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) has been the subject of much controversy. Major international guidelines recommend selective use of ICS. Recently published meta-analyses have reported conflicting findings on the effects of inhaled steroid therapy in COPD.

Objectives

To determine the efficacy and safety of inhaled corticosteroids in stable patients with COPD, in terms of objective and subjective outcomes.

Search methods

A pre-defined search strategy was used to search the Cochrane Airways Group Specialised Register for relevant literature. Searches are current as of July 2011.

Selection criteria

We included randomised trials comparing any dose of any type of inhaled steroid with a placebo control in patients with COPD. Acute bronchodilator reversibility to short-term beta$_2$-agonists and bronchial hyper-responsiveness were not exclusion criteria. The a priori primary outcome was change in lung function. We also analysed data on mortality, exacerbations, quality of life and symptoms, rescue bronchodilator use, exercise capacity, biomarkers and safety.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We contacted study authors for additional information. We collected adverse effects information from the trials.

Main results

Fifty-five primary studies with 16,154 participants met the inclusion criteria. Long-term use of ICS (more than six months) did not consistently reduce the rate of decline in forced expiratory volume in one second (FEV_1) in COPD patients (generic inverse variance analysis: mean difference (MD) 5.80 mL/year with ICS over placebo, 95% confidence interval (CI) -0.28 to 11.88, 2333 participants; pooled means analysis: 6.88 mL/year, 95% CI 1.80 to 11.96, 4823 participants), although one major trial demonstrated a statistically significant difference. There was no statistically significant effect on mortality in COPD patients (odds ratio (OR) 0.98, 95% CI 0.83 to 1.16, 8390 participants). Long-term use of ICS reduced the mean rate of exacerbations in those studies where pooling of data was possible (generic inverse

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variance analysis: MD -0.26 exacerbations per patient per year, 95% CI -0.37 to -0.14, 2586 participants; pooled means analysis: MD -0.19 exacerbations per patient per year, 95% CI -0.30 to -0.08, 2253 participants). ICS slowed the rate of decline in quality of life, as measured by the St George's Respiratory Questionnaire (MD -1.22 units/year, 95% CI -1.83 to -0.60, 2507 participants). Response to ICS was not predicted by oral steroid response, bronchodilator reversibility or bronchial hyper-responsiveness in COPD patients. There was an increased risk of oropharyngeal candidiasis (OR 2.65, 95% CI 2.03 to 3.46, 5586 participants) and hoarseness. In the long-term studies, the rate of pneumonia was increased in the ICS group compared to placebo, in studies that reported pneumonia as an adverse event (OR 1.56, 95% CI 1.30 to 1.86, 6235 participants). The long-term studies that measured bone effects generally showed no major effect on fractures and bone mineral density over three years.

Authors' conclusions

Patients and clinicians should balance the potential benefits of inhaled steroids in COPD (reduced rate of exacerbations, reduced rate of decline in quality of life and possibly reduced rate of decline in FEV_1) against the potential side effects (oropharyngeal candidiasis and hoarseness, and risk of pneumonia).

PLAIN LANGUAGE SUMMARY

Inhaled steroids for stable chronic obstructive pulmonary disease

Steroid preventer medications given by inhaler ('inhaled steroids') help to reduce inflammation in the air passages of people with asthma. However, it is uncertain whether these medications are beneficial in people with chronic obstructive pulmonary disease (COPD, i.e. chronic bronchitis or emphysema or both).

We undertook a systematic review of the benefits and safety of inhaled steroids for people with COPD. Our review analysed the effects on breathing capacity, death rates, frequency of flare-ups ('exacerbations'), quality of life and side effects.

Pooling of the data from the 55 trials with 16,154 people showed that there was no consistent long-term benefit in the rate of decline in breathing capacity. Death rates were unchanged. Inhaled steroids were beneficial in slowing down the rate of decline in quality of life and reducing the frequency of exacerbations. Inhaled steroids increased the risk of side effects including thrush (candida) infection in the mouth and hoarseness, and the rate of pneumonia.

In deciding whether to use this treatment, consumers and health professionals should weigh up the benefits (reduced rate of exacerbations, reduced decline in quality of life and possible reduction in the rate of decline of breathing capacity) against the side effects (mouth thrush, hoarseness and increased risk of developing pneumonia).

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BACKGROUND

Inhaled corticosteroids (ICS) have proven benefit in the treatment of airway inflammation in asthma, but there are still questions about their use in patients with chronic obstructive pulmonary disease (COPD). The Global Initiative for Obstructive Lung Disease (GOLD) guidelines for COPD recommend adding ICS to long-acting beta$_2$-agonists for symptomatic COPD patients with forced expiratory volume in one second (FEV_1) less than 50% predicted and repeated exacerbations (GOLD COPD guidelines, www.goldcopd.org). The rationale for use of ICS in COPD has been discussed extensively in editorials (van Schayck 1996; Calverley 1999; Mapp 2000; Burge 2003b; Epstein 2003; Woodhead 2007; Welte 2009; Sin 2010), pro/con debates (Barnes 2000; Calverley 2000), narrative reviews (Hudson 1990; Postma 1999; Sapey 2000; Whittaker 2000; Burge 2001;; Bonay 2002; Highland 2004; Selroos 2004; Bonay 2005; Calverley 2005; Man 2005b) and systematic reviews (van Grunsven 1999; Alsaeedi 2002; Highland 2003; Sin 2003b; Sin 2003c; Sutherland 2003; Gan 2005; Sin 2005; Gartlehner 2006; Soriano 2007; Drummond 2008; Sin 2009; Singh 2009; Agarwal 2010; Loke 2011). As the effectiveness and safety of ICS in COPD patients are still contentious, we undertook this updated Cochrane systematic review of ICS for COPD.

OBJECTIVES

To determine the efficacy and safety of inhaled corticosteroids in stable patients with COPD, in terms of objective and subjective outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all published and unpublished randomised controlled trials (RCTs) of regular ICS in COPD. Placebo-controlled trials with random allocation and double-blinding were included. We preferred trials analysed on an intention-to-treat basis. We considered parallel-group and cross-over studies.

Types of participants

We reviewed studies of adults of either gender, regardless of smoking history, with COPD defined as progressive chronic airflow limitation. Patients were in a clinically stable state at the start of the study, without recent exacerbation, hospitalisation or need for antibiotics or systemic steroids. Patients did not have clinical features of asthma. Studies recruiting patients with acute bronchodilator reversibility to short-acting beta$_2$-agonists or patients with bronchial hyper-responsiveness (BHR) were included. We analysed these BHR studies separately from studies of COPD patients in which BHR was not an inclusion criteria or in which BHR was excluded.

Types of interventions

We included studies of regular ICS administered by inhalation devices including metered-dose inhaler, dry powder inhaler or spacer devices. We excluded studies delivering ICS by nebuliser. We did not include ICS versus placebo with long-acting beta$_2$-agonists as a co-intervention in each group.

Types of outcome measures

Primary outcomes

1. Lung function

Secondary outcomes

1. Mortality
2. Exacerbations of COPD
3. Quality of life and symptoms
4. Use of rescue bronchodilators
5. Exercise capacity
6. Biomarkers
7. Predictors of response
8. Side effects: oropharyngeal side effects (throat irritation, oral candidiasis), skin bruising, hypothalamic-pituitary-adrenal (HPA) axis function, fractures, pneumonia

Search methods for identification of studies

Electronic searches

In the original review, we examined and combined randomised controlled trials of inhaled corticosteroids in adults with COPD from 1966 to October 2006. The 2011 update includes trials from October 2006 to July 2011. Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (see Appendix 1 for more details). We searched all records in the Specialised Register coded as 'COPD' using the following terms:

(corticosteroid* or cortico-steroid* or beclomethasone or beclazone or becotide or becloforte or budesonide or pulmicort* or fluticasone or flixotide or qvar or zonivent or filair or aerobec or asmabec or becodisk* or triamcinolone or mometasone or flunisolide)

Searching other resources

We searched the bibliographies of each included study for additional relevant studies. We undertook additional searches of manufacturers' websites in order to identify unpublished data (http://ctr.gsk.co.uk; http://www.astrazenecaclinicaltrials.com/; http://www.clinicalstudyresults.org).

Data collection and analysis

Selection of studies

Two review authors independently assessed for relevance the titles and, where available, abstracts of all trials retrieved by the search strategy. We then retrieved all relevant or potentially relevant articles in full. We categorised these articles as relevant (met the inclusion criteria for considering studies) or not relevant (did not meet the inclusion criteria for considering studies). We resolved disagreements about relevance by consensus.

Data extraction and management

Three review authors (IY, ES and TL) extracted data from included studies for the original review, and two review authors (IY, MC) extracted data from included studies for the 2011 update. Wherever

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possible, we sought missing data in the publication from the authors by correspondence (email, fax or letter).

Assessment of risk of bias in included studies

Two review authors independently assessed the quality of all relevant trials, using the Cochrane approach, to assess risk of bias.

Measures of treatment effect

If appropriate data for mean, standard deviation (SD) and number of participants in each treatment and placebo arm were available, we combined data from trials using Review Manager 5 (RevMan 2011), generating a mean difference and 95% confidence interval. We used a mean difference (MD) for continuous variables. We summarised proportional outcomes, such as proportion who improved, using an odds ratio. We used the Mantel-Haenszel method to combine estimates of the odds ratios.

Assessment of heterogeneity

We performed tests for heterogeneity using Review Manager 5. We also applied a random-effects model as part of sensitivity analysis.

Assessment of reporting biases

A funnel plot of studies will be created if 10 or more trials are included in any single meta-analysis comparison.

Data synthesis

We used a fixed-effect mean difference (MD) for continuous variables. If data were reported on different metrics, we planned to use a standardised mean difference (SMD), which expresses differences as standard deviation units.

Subgroup analysis and investigation of heterogeneity

The treatment periods were separated into short-term (less than two months), medium-term (greater than two months to six months) and long-term (greater than six months). We stratified data by equivalent beclomethasone dosage.

RESULTS

Description of studies

Results of the search

We retrieved and assessed a total of 2205 abstracts in the original review. In the 2011 update, we retrieved and assessed 339 additional abstracts (see Table 1: 'Search history detail'), with 36 studies meeting the inclusion criteria; of these, eight were new studies not previously included. A total of 55 studies (compared to 47 studies in the original review) met the inclusion criteria for the systematic review. For full details on individual studies, please see 'Characteristics of included studies'

Included studies

Study design

All studies were randomised, placebo-controlled trials. All studies were described as either double-blind or double-dummy. Thirteen studies were of a cross-over design (Robertson 1986; Weir 1990a; Wempe 1992; Weiner 1995; Boothman-Burrell 1997; Culpitt 1999; Nishimura 1999; Weiner 1999; Ferreira 2001; Loppow 2001; Thompson 2002; Brightling 2005; Guenette 2011). The remaining studies were conducted with a parallel-group design.

Participants

A total of 16,154 participants (13,139 in the original review) with COPD were recruited in the studies. More recent trials tended to use international criteria for the definition of COPD, and the remaining studies based their definition of COPD on lung function and smoking history (see table: 'Characteristics of included studies'). The entry criteria differed between the studies in terms of permissible bronchial hyper-responsiveness (BHR) or bronchodilator reversibility; hence we stratified studies by whether COPD patients with these features were included. The majority of studies excluded participants who had an exacerbation within six to eight weeks prior to recruitment.

Interventions

All studies were placebo-controlled. There were five types of inhaled steroid used in the trials: BUD (budesonide), BDP (beclomethasone dipropionate), FP (fluticasone propionate), TAA (triamcinolone acetonide) and mometasone furoate (MF). Study durations were as follows.

Up to two months in 18 studies (Robertson 1986; Weir 1990a; Auffarth 1991; Thompson 1992; Wempe 1992; Weiner 1995; Llewellyn-Jones 1996; Rutgers 1998; Culpitt 1999; Nishimura 1999; Weiner 1999; Ferreira 2001; Loppow 2001; Ferreira 2003; Sin 2004; Brightling 2005; Sin 2008; Guenette 2011).

Longer than two months and up to six months in 17 studies (Boothman-Burrell 1997; Bourbeau 1998; Paggiaro 1998; Senderovitz 1999; Mirici 2001; Hattotuwa 2002; Laptseva 2002; Mahler 2002; Thompson 2002; Verhoeven 2002; Hanania 2003; Yildiz 2004; John 2005; Ozol 2005; GSK 2005 (FCO30002); GSK 2005 (FLTA3025); Bourbeau 2007).

Longer than six months in 20 studies (Kerstjens 1992; Derenne 1995; Renkema 1996; Pauwels 1999; Vestbo 1999; Weir 1999; Burge 2000; LHS 2000; Calverley 2003a; Calverley 2003b; Calverley 2003c; Szafranski 2003; van Grunsven 2003; SCO30002 2005; Calverley 2007; Calverley 2008; Tashkin 2008; Lapperre 2009; Schermer 2009; Shaker 2009).

Outcomes

Various outcomes were measured in the studies (see tables 'Characteristics of included studies'). The long-term studies (more than six months) reported FEV_1 in terms of rate of decline, and short to medium-term studies tended to report change in FEV_1 from baseline. Exacerbations were variously reported as dichotomous data (e.g. patients with one or more exacerbations), exacerbation episodes per treatment arm, or mean rate per patient per year. Some studies measured quality of life, symptoms and rescue bronchodilator usage. A group of studies specifically focused on changes in biomarkers (for example, sputum analysis). Long-term studies also analysed adverse effects.

Excluded studies

See Characteristics of excluded studies.

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Risk of bias in included studies

The quality of published studies was generally good, although many studies had unclear risk of bias in relation to randomisation method and allocation concealment. Unpublished abstracts generally has greater risk of bias, due to lack of details in reporting. See Figure 1.

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Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

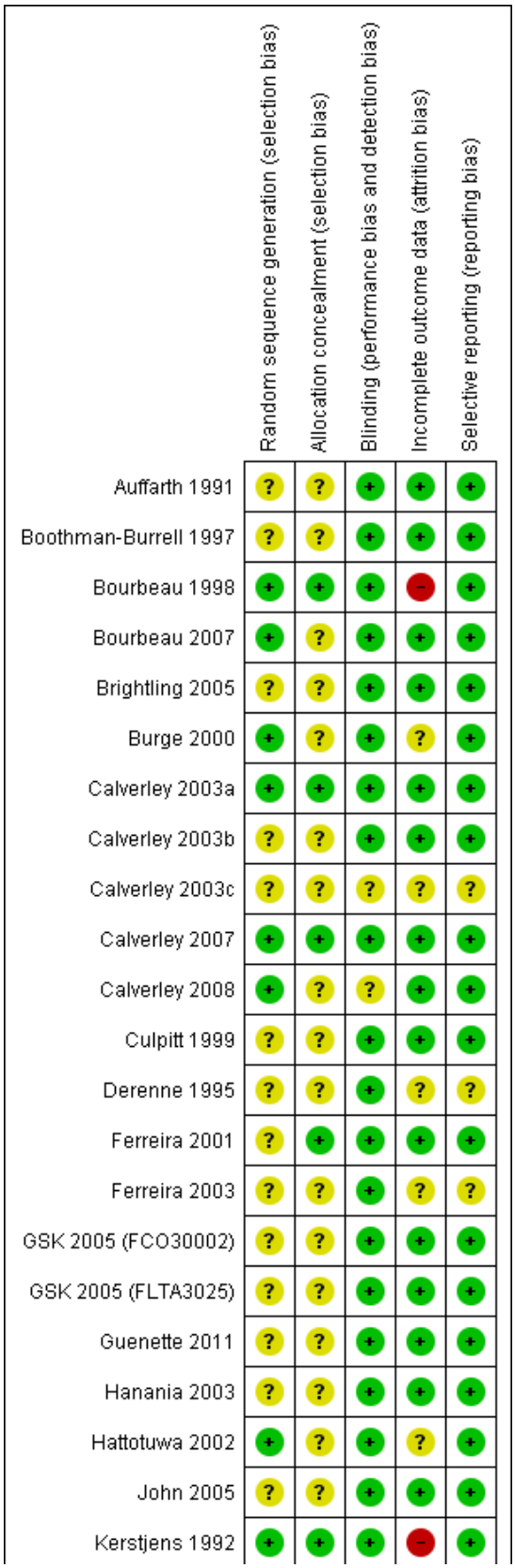

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Figure 1. (Continued)

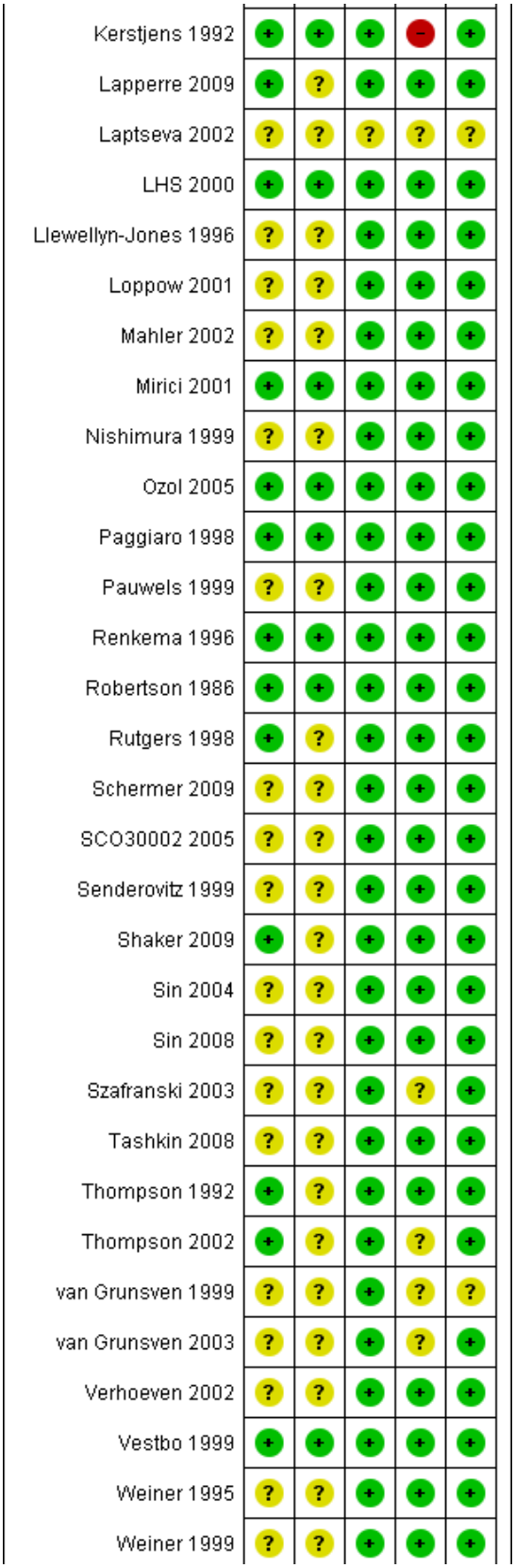

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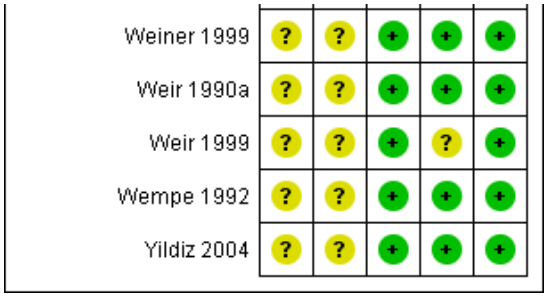
Figure 1. (Continued)



Allocation

Studies used random allocation. However, many studies did not specifically state the randomisation method, or whether allocation was concealed.

Blinding

All published studies were double-blind. Several studies presented in abstract form did not specifically state whether the study was double-blind.

Incomplete outcome data

The attrition rate was acceptable in the majority of studies. For studies with higher attrition rates, the studies provided adequate detail about the rates of withdrawal in the ICS and placebo arms.

Selective reporting

The published included studies reported the outcomes listed a priori in their methods. This was difficult to ascertain for studies presented in abstract form.

Effects of interventions

Studies in people with COPD (without bronchial hyper-responsiveness or bronchodilator reversibility)

Long-term studies (longer than six months)

Three-year studies

Six large, long-term trials of ICS versus placebo were reported in COPD participants without bronchial hyper-responsiveness or bronchodilator reversibility. All were parallel studies. In the European Respiratory Society Study on COPD (EUROSCOP) study, Pauwels et al studied 1277 participants with BUD 800 µg/day versus placebo for three years (Pauwels 1999). The participants were current smokers with mild COPD, with mean FEV_1 77% predicted. In the initial six months of the study, BUD resulted in an increase in FEV_1 of 17 mL/year compared to a decline of 81 mL/year in the placebo group. After the initial six months, the rates of decline in FEV_1 were similar.

The study from Copenhagen reported by Vestbo et al used BUD 1200 µg/day for six months then 800 µg/day for 30 months (total three years) versus placebo in 290 participants (Vestbo 1999). The sample was population-based and participants were recruited if they had a FEV_1/VC ratio of 0.7 or less without bronchodilator reversibility or oral steroid response. Forty per cent of participants stated that they had no breathing problems and 4% were never smokers. Mean post-bronchodilator FEV_1 was 86% to 87% predicted. There was no statistically significant effect of BUD on rate of decline in FEV_1, rate of exacerbations or symptoms.

In the ICS in Obstructive Lung Disease in Europe (ISOLDE) study, Burge et al randomised 751 participants to FP 1000 µg/day versus placebo for three years (Burge 2000). This was a moderate to severe group of participants, with mean FEV_1 50% of predicted. All were current or ex-smokers. The majority of participants received a two-week oral prednisolone course during the run-in. FP did not alter the rate of overall rate of decline of FEV_1, although the mean FEV_1 of the FP group remained about 70 mL higher than the placebo group throughout the study. FP reduced the median exacerbation rate (Burge 2000), particularly in the moderate-severe group of participants (Jones 2003). FP also slowed the decline in health status as determined by the St George's Respiratory Questionnaire (SGRQ) (Spencer 2001).

The Lung Health Study II enrolled 1116 participants and randomised them to inhaled triamcinolone (TAA) 1200 µg/day versus placebo for a mean duration of follow-up of 40 months (Lung Health Study Research Group 2000). Mean FEV_1 was 64% predicted and all were current smokers or ex-smokers. The rate of decline in FEV_1 was similar in the TAA and placebo groups. TAA reduced respiratory symptoms and visits to doctors for respiratory illnesses. TAA also lowered the airway reactivity to methacholine over the course of treatment.

The large TOwards a Revolution in COPD Health (TORCH) study recruited 6115 participants and randomised them to salmeterol/fluticasone, salmeterol, FP 1000 µg/day (1534 participants) and placebo (1524 participants). In the FP versus placebo comparison, there was a reduction in COPD exacerbation rate, with odds ratio (OR) 0.823 (95% confidence interval (CI) 0.758 to 0.894) (Calverley 2007). No mortality benefit was observed with FP alone compared to placebo, with hazard ratio 1.060 (95% CI 0.886 to 1.268) (Ferguson 2006). There was a benefit in quality of life measured by the SGRQ, with a difference of -2.0 units (95% CI -2.9 to -1.0) with FP, compared to placebo. The rate of FEV_1 decline was slower in the FP group compared to placebo (difference 13 mL/year, 95% CI 5 to 22) (Celli 2008).

The COOPT trial recruited 286 participants (78% COPD, 22% chronic bronchitis) from 44 general practices and randomised them to FP 500 µg twice daily or placebo for three years (N-acetylcysteine was used in a separate arm) (Schermer 2009). Exacerbation rate was 1.3 times higher for the FP group compared with the placebo group, although this did not reach statistical significance. Annual decline in post-bronchodilator FEV_1 was similar between groups.

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Two-year studies

Four parallel studies of two years duration have been performed in COPD participants without bronchial hyper-responsiveness or bronchodilator reversibility (Derenne 1995; Renkema 1996; Weir 1999; Lapperre 2009). The study by Derenne was reported in abstract form (Derenne 1995) and summarised in the meta-analysis by van Grunsven et al (van Grunsven 1999). Renkema et al studied 39 participants with BUD 1500 µg/day versus placebo for two years (Renkema 1996). They observed a reduced rate of decline in FEV_1 (although this was not statistically significant) and reduced symptoms with BUD alone versus placebo. There was no change in rate of exacerbations (Renkema 1996). Weir et al studied 98 participants using BDP 1500 µg/day versus placebo for two years (Weir 1999). There were trends to benefits with BDP in terms of decline in FEV_1 and exacerbation rates but these did not reach statistical significance. There was no change in BHR to histamine or dyspnoea as measured by the Mahler dyspnoea index. The data from COPD subgroups of the study by Kerstjens et al, which included COPD participants with BHR (Kerstjens 1992), and Derenne (Derenne 1995) were combined with the data from Renkema (Renkema 1996) in the meta-analysis by van Grunsven et al (van Grunsven 1999) (see 'Discussion' for details). Lapperre et al randomised 114 participants with moderate to severe COPD to FP 500 µg twice daily for six months or 30 months, or placebo twice daily (salmeterol/fluticasone was used in a separate arm) (Lapperre 2009). FP for 30 months was found to slow the rate of FEV_1 decline, and improve dyspnoea and quality of life. A small four-year trial studied the effect of inhaled corticosteroids on lung density in COPD (Shaker 2009). Shaker et al demonstrated that inhaled BUD 800 µg daily over two to four years showed a non-significant trend towards reducing the progression of emphysema as determined by the CT-derived 15th percentile lung density, without any statistically significant effect on decline in lung function (Shaker 2009).

One-year studies

Four parallel studies of combined ICS/long-acting $beta_2$-agonist (LABA) in COPD included ICS versus placebo arms. In the one-year TRISTAN study of salmeterol/FP, salmeterol, FP or placebo by Calverley et al in 1465 participants, data were available for FP 1000 µg/day versus placebo in one of the comparisons (Calverley 2003a). FP increased pre-bronchodilator FEV_1 by 2%, compared to a fall of 3% with placebo at one year, and reduced the mean exacerbation rate of 1.3 in the placebo group to 1.05 in the FP group. There was no significant change in SGRQ total score or symptom scores with FP compared to placebo, although FP reduced the use of relief medications and awakenings per week (Calverley 2003a). Szafranski et al studied BUD/formoterol, BUD, formoterol or placebo in 812 COPD participants for one year (Szafranski 2003). Small but statistically significant benefits were observed with BUD 800 µg/day compared to placebo for lung function changes and exacerbation rates. Calverley et al similarly studied these medications in 1022 COPD participants for one year, and found fewer exacerbations with BUD compared to placebo, and no significant difference in FEV_1 (Calverley 2003b). An unpublished study of salmeterol/FP in COPD (GlaxoSmithKline trial SCO30002 2005) included a comparison of FP 1000 µg/day versus placebo in 256 COPD participants (SCO30002 2005). There was no statistically significant difference in time to first moderate or severe exacerbation with FP or change in post-bronchodilator FEV_1.

Two parallel studies of MF for one year duration have been reported. A study of MF 800 µg/day versus placebo in 631 COPD participants was reported in abstract form (Calverley 2003c). MF was associated with a benefit in post-bronchodilator FEV_1 of 40 mL, compared to placebo, reduced COPD symptoms and increased time to first exacerbation. Calverley et al randomised 911 participants with moderate to severe COPD to MF-DPI 800 µg once daily, MF-DPI 400 µg twice daily or placebo (Calverley 2008). MF-DPI significantly increased post-bronchodilator FEV_1 from baseline and reduced exacerbations. The twice daily MF-DPI group reported a statistically significant reduction (19%) in COPD symptoms scores compared with placebo. SGRQ improved significantly in all domains in the pooled MF-DPI groups versus placebo.

Pooled results

Lung function

In the studies of two years or longer, we analysed the main treatment effect of change in rate of FEV_1 decline. Two approaches to analysing rate of decline of post-bronchodilator FEV_1 were used, due to the various ways the data were presented in the studies.

When analysing data using the generic inverse variance function of RevMan 5 (RevMan 2011), the pooled difference in rate of decline in post-bronchodilator FEV_1 in four studies (Vestbo 1999; Weir 1999; Burge 2000; LHS 2000) and one combined result (van Grunsven 1999) was 5.80 mL/year with ICS (95% CI -0.28 to 11.88; 2333 participants) (Figure 2). In the study by Pauwels et al (1277 participants), there was no significant difference between the median decline of FEV_1 of -57 mL/year in the budesonide group, compared to the -69 mL/year in the placebo group (Pauwels 1999).

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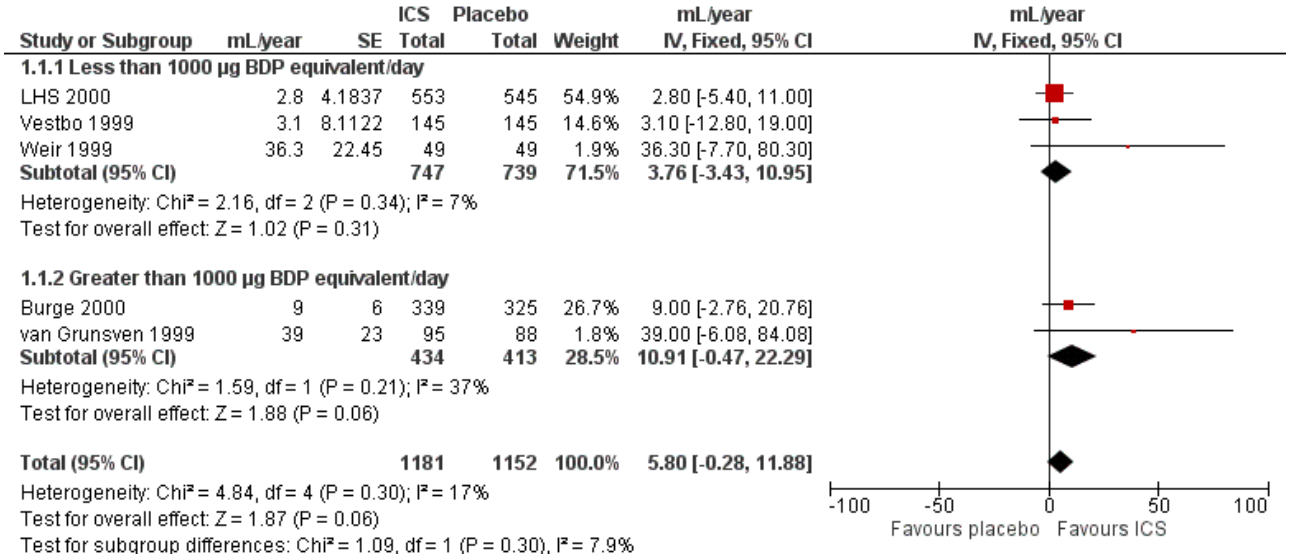
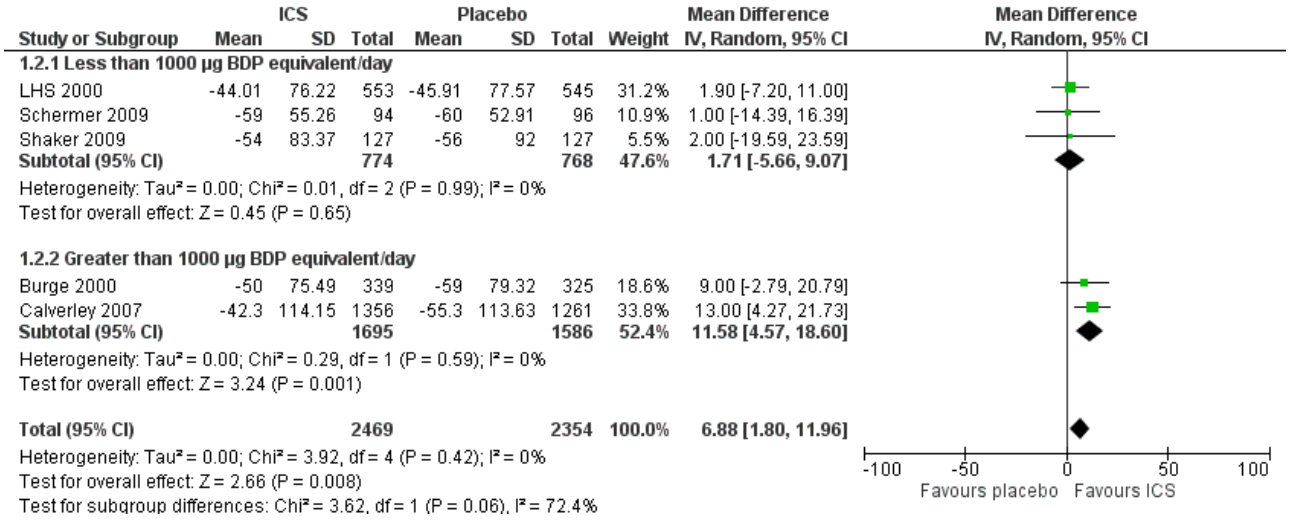
Figure 2. Forest plot of rate of decline of post-bronchodilator FEV_1 (mL/yr), using generic inverse variance analysis



When analysing means for the ICS versus placebo groups, the pooled difference in rate of decline in post-bronchodilator FEV_1 in five studies (Burge 2000; LHS 2000; Celli 2008; Schermer 2009; Shaker 2009) was 6.88 mL/year (95% CI 1.80 to 11.96, 4823 participants) (Figure 3). The main contributor to this statistically significant difference was the TORCH study, which showed a difference for the ICS alone (fluticasone 1000 µg/day, 42 mL/year decline) versus placebo (55 mL/year decline) (Celli 2008). In the TORCH trial, salmeterol (42 mL/year decline) and salmeterol/fluticasone (39 mL/year decline) also had similar benefits in rate of decline in FEV_1 (Celli 2008). The study of Lapperre 2009 demonstrated a statistically significant difference in rate of decline of FEV_1 (mean difference 86.30 mL/year, 95% CI 43.02 to 129.58); however, this result was not pooled because the rate of decline measured was from six months to 30 months of treatment, instead of from 0 months.

Figure 3. Forest plot of rate of decline in post-bronchodilator FEV_1 (mL/yr), using pooled means analysis



In the studies of one year duration, improvements with ICS were reported for pre-bronchodilator FEV_1 (Szafranski 2003) and post-bronchodilator FEV_1 (Calverley 2003b; Calverley 2003c; Calverley 2008). In one study, there was no significant difference (SCO30002 2005) and one study did not report the spirometry results specifically for the inhaled steroid versus placebo comparison (Calverley 2003a).

Mortality

Mortality was reported in nine long-term studies (Figure 4). The overall OR for mortality for all nine studies was 0.98 (95% CI 0.83 to 1.16, 8390 participants). In studies of one-year duration (Calverley 2003a; Calverley 2003b; Szafranski 2003; SCO30002 2005) pooling showed an OR of 0.66 for death with ICS compared to placebo (95% CI 0.33 to 1.31, 1907 participants). In studies of two or more years duration, pooling showed an OR of 1.01 for death with ICS

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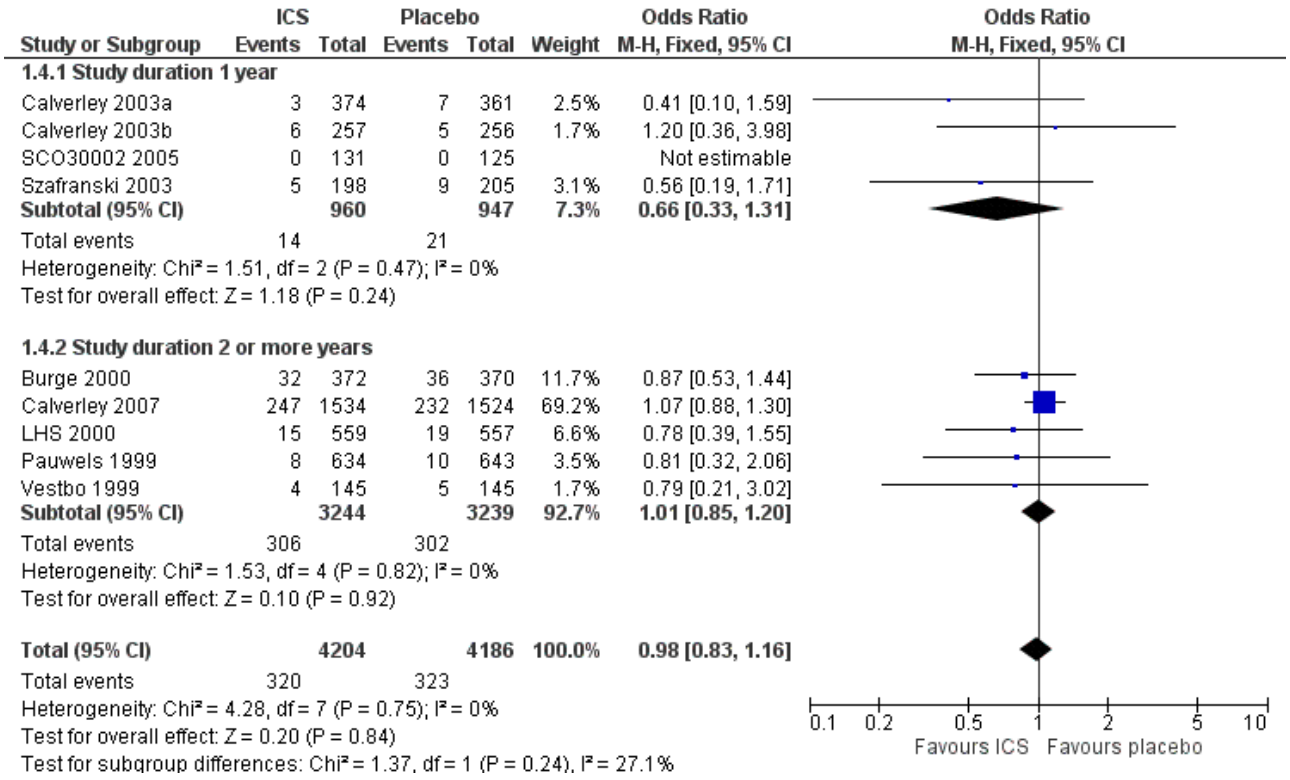
compared to placebo (95% CI 0.85 to 1.20, 6483 participants) (Pauwels 1999; Vestbo 1999; Burge 2000; LHS 2000; Calverley 2007).

Figure 4. Forest plot of mortality in long-term studies



Exacerbations

Using the generic inverse variance function, pooling was possible for four long-term studies (Burge 2000; Calverley 2003a; Calverley 2003b; Szafranski 2003) and the meta-analysis of three long-term studies (van Grunsven 1999). The mean difference (MD) for this analysis was -0.26 exacerbations per patient per year with ICS (95% CI -0.37 to -0.14; 2586 participants) (Comparison 1.5) (Figure 5). We also pooled mean rate of exacerbation per patient per year using data from treatment and control groups from four long-term studies (Burge 2000; Calverley 2003a; Szafranski 2003; Schermer 2009) and a combined rate from the van Grunsven et al meta-analysis of three long-term studies (van Grunsven 1999). The MD was -0.19 exacerbations per patient per year with ICS (95% CI -0.30 to -0.08, 2253 participants) (Comparison 1.6) (Figure 6). The study of Schermer 2009 found an increased exacerbation rate with ICS, whereas the other studies had reduced exacerbation rates with ICS.

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Figure 5. Forest plot of exacerbations per patient per year, using generic inverse variance analysis

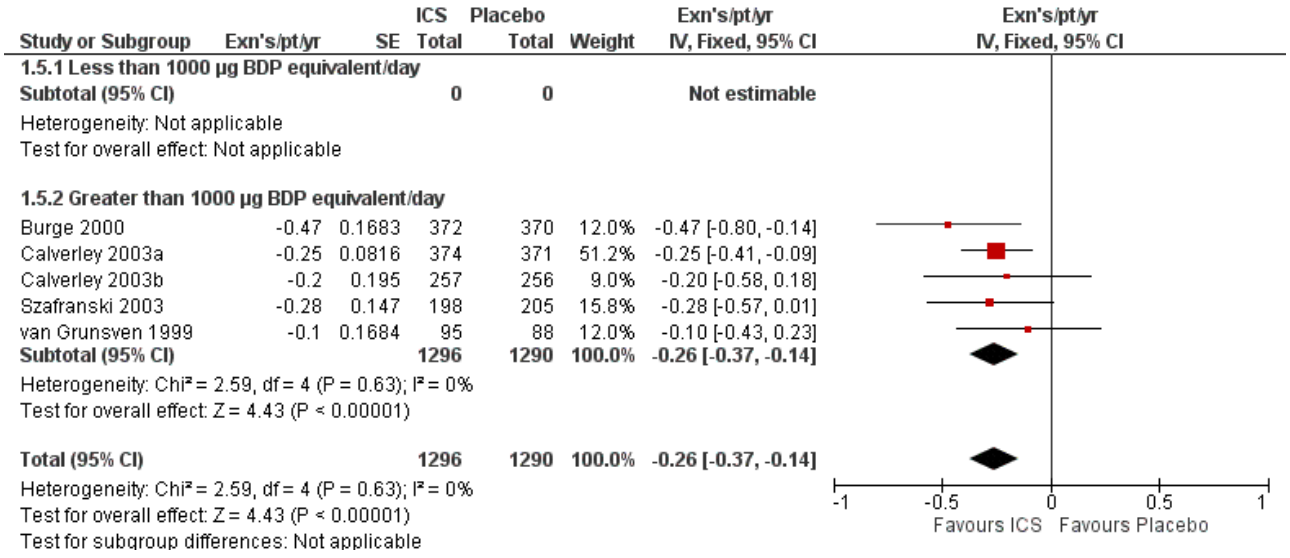
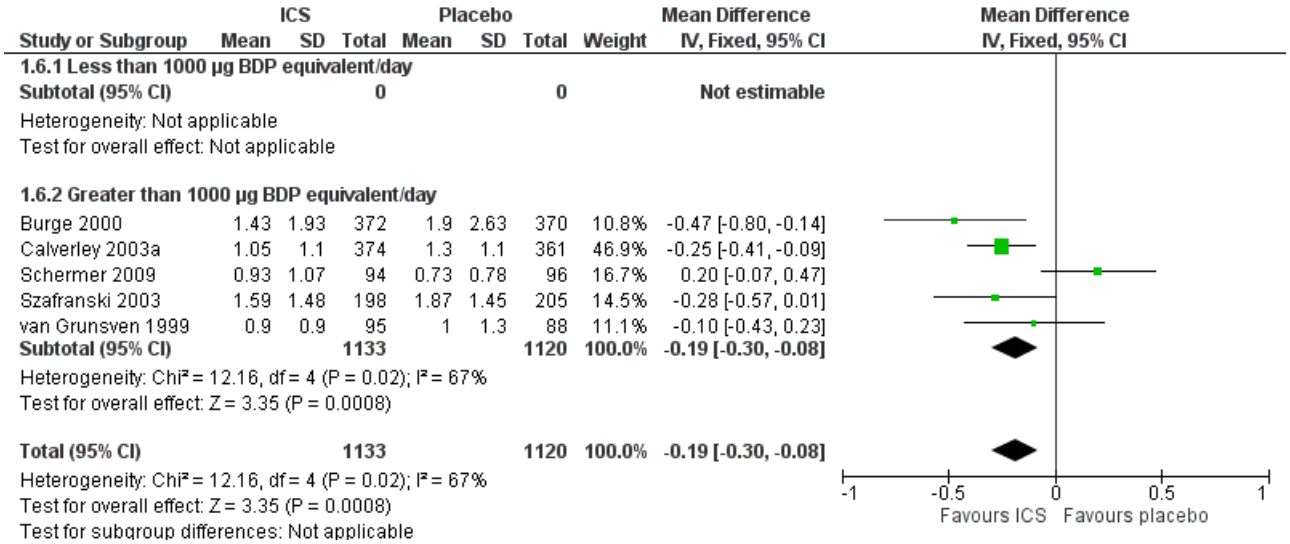


Figure 6. Forest plot of rate of exacerbations per patient per year, using pooled means analysis



In other long-term studies, exacerbation events were not reported in sufficient detail to pool as mean rate of exacerbation per patient per year. The results of these studies were: no significant difference in mean exacerbation rates per year between BDP (0.36/year) and placebo (0.57/year) (Weir 1999), no significant difference in total number of exacerbations between BUD (155 exacerbations) and placebo (161 exacerbations) (Vestbo 1999), and reduced number of unscheduled physician visits and hospitalisation for respiratory conditions (data not stated) (LHS 2000). In one unpublished study, the total number of exacerbations was reported without analysis being performed, with 123 exacerbations in the FP group and 127 exacerbations in the placebo group (SCO30002 2005). In the TORCH study, the mean number of exacerbations per year was 0.93 in the FP group, compared to 1.13 in the placebo group, giving a statistically significant rate ratio of 0.82 (95% CI 0.76 to 0.89) (Calverley 2007). The EUROSCOP study did not report exacerbation rates (Pauwels 1999).

Four studies reported percentage of participants with at least one exacerbation (Comparison 1.8). Pooling of these results showed an OR of 0.83 in favour of ICS (95% CI 0.7 to 0.98, 2347 participants). Studies of less than 1000 µg BDP equivalent/day (Calverley 2008; Shaker 2009) did not show a statistically significant difference. However, studies of greater than 1000 µg/day (Calverley 2003c; SCO30002 2005; Calverley 2008) did show a statistically significant reduced percentage of patients with exacerbations (OR 0.8, 95% CI 0.65 to 0.98) with low heterogeneity (I^2 = 0%), although none of these studies were statistically significant individually.

Quality of life and symptoms

Pooling of rate of change in SGRQ in units/year was analysed with the generic inverse variance function in five long-term studies (Burge 2000; Calverley 2003a; Calverley 2003b; Szafranski 2003; SCO30002 2005). The MD was -1.22 units/year (95% CI -1.83 to -0.60, 2507 participants), indicating a slowing in the rate of decline of

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quality of life in the ICS group, compared to placebo (Comparison 1.10). There was no improvement in SF-36 with ICS (LHS 2000). The TORCH study reported a mean benefit in SGRQ of -2.0 units averaged over three years (95% CI -2.9 to -1.0) with FP compared to placebo (Calverley 2007).

Data for symptoms were mostly not presented in sufficient detail to pool. Symptom scores in general decreased with ICS (Renkema 1996; Calverley 2003c;), and night awakenings were reduced (Calverley 2003b). In one study, there was no change in dyspnoea score measured by the Mahler dyspnoea index (Weir 1999).

Use of rescue bronchodilators

Only one long-term study analysed rescue bronchodilator use. In this study, there was no significant difference in use of reliever medication with ICS (Calverley 2003b).

Exercise capacity

Shuttle walking test was measured in one long-term study (SCO30002 2005) but there was insufficient detail provided in order to analyse for statistical significance.

Medium-term studies (longer than two months and up to six months)

Three-month studies

Parallel studies

Mirici et al studied 40 participants using BUD 800 µg/day versus placebo for 12 weeks (Mirici 2001). FEV_1 and forced vital capacity (FVC) increased significantly with BUD treatment compared to placebo, despite no change in sputum inflammatory neutrophil or eosinophil counts. Hattotuwa et al randomised 31 participants to FP 1000 µg/day versus placebo for three months in a biopsy study (Hattotuwa 2002). Although no significant differences in lung function or dyspnoea were found, FP improved cough and sputum, and reduced reliever medication use, and there was a reduction in exacerbation rate. Yildiz et al studied 38 participants using BUD 800 µg/day versus placebo (Yildiz 2004). Total and activity scores of the SGRQ improved with BUD, without changes in spirometry or arterial blood gases. In a biopsy study, Bourbeau et al randomised 60 participants to a combination of 50 µg salmeterol and 500 µg FP twice daily, or 500 µg FP twice daily, or placebo (Bourbeau 2007). There was no difference in lung function or health-related quality of life at three months. One unpublished study (GSK 2005 (FCO30002)) randomised 217 participants from multiple centres to placebo tablets (two weeks) followed by FP 500 µg twice daily (12 weeks), or prednisolone 20 to 40 mg daily plus placebo inhaler (two weeks) followed by FP 500 µg twice daily (10 weeks), or placebo tablets (two weeks) followed by placebo inhaler (12 weeks). There was no statistically significant difference in change in FEV_1 in the ICS versus placebo groups.

Cross-over studies

John et al performed a cross-over study of 11 participants using HFA-BDP 800 µg/day versus placebo (John 2005). With HFA-BDP, spirometry remained unchanged, hyperinflation was reduced (RV/TLC%), and quality of life improved (SGRQ).

Six-month studies

Parallel studies

Bourbeau et al used BUD 1600 µg/day versus placebo in 79 COPD participants who were non-responders to oral steroids (Bourbeau 1998). They found no significant differences in lung function, six-minute walk test, symptoms or quality of life (Chronic Respiratory Questionnaire) with BUD compared to placebo. Paggiaro et al studied 281 participants using FP 1000 µg/day versus placebo. FP treatment was associated with a reduced rate of moderate-severe exacerbations, improved peak expiratory flow rate (PEFR) and FEV_1, increased six-minute walk distance, and improvement in diary card symptoms (Paggiaro 1998). Senderovitz et al studied BUD 800 µg/day versus placebo in 40 participants and observed no significant differences in median post-bronchodilator FEV_1, exacerbations or symptom scores (Senderovitz 1999). In a study published in abstract form, Laptseva et al treated 49 participants with BUD 800 µg/day versus placebo, and found reduction in moderate-severe exacerbation rate and improvement in FEV_1 (Laptseva 2002). Mahler et al studied 691 participants using FP 1000 µg/day or placebo for 24 weeks (Mahler 2002). FP alone improved FEV_1, PEFR, dyspnoea, salbutamol use, night awakenings and quality of life (Chronic Respiratory Disease Questionnaire, Chronic Bronchitis Symptoms Questionnaire (CBSQ)) compared to placebo (Mahler 2002). In a similar study design using half the FP dose (500 µg/day), Hanania et al showed similar results (Hanania 2003). In a biomarker study of BUD 800 µg/day versus placebo in 26 participants, Ozol et al found no improvement in post-bronchodilator FEV_1 or FVC (Ozol 2005). In an unpublished study of 640 participants, there was a statistically significant improvement in pre-bronchodilator FEV_1 for FP 500 µg twice daily versus placebo (GSK 2005 (FLTA3025)), however, this was not shown in the FP 250 µg twice daily group. Tashkin 2008 studied BUD 640 µg/day versus placebo for six months (and included other arms), and found that BUD did not significantly change FEV_1 but reduced exacerbations, compared to placebo.

Pooled results

Lung function

Using the generic inverse variance function, we performed pooling for change in pre-bronchodilator FEV_1 in seven medium-term studies (Bourbeau 1998; Hattotuwa 2002; Mahler 2002; Hanania 2003; GSK 2005 (FCO30002); GSK 2005 (FLTA3025); Tashkin 2008). The mean change in FEV_1 was MD 0.04 L in favour of ICS (95% CI 0.03 to 0.06) (Comparison 2.1). Pooling of change in post-bronchodilator FEV_1 from four medium-term studies (Paggiaro 1998; Mahler 2002; Hanania 2003; Tashkin 2008) showed MD 0.11 L in favour of ICS (95% CI 0.07 to 0.16) (Analysis 2.4). Other studies could not be pooled due to presentation of data as per cent increase (Mirici 2001), pre-treatment and post-treatment (Yildiz 2004; John 2005; Ozol 2005), medians (Senderovitz 1999) or summary statement without data (Laptseva 2002).

Mortality

Mortality was reported in five medium-term studies (Hattotuwa 2002; Mahler 2002; Hanania 2003; GSK 2005 (FCO30002); GSK 2005 (FLTA3025)). Pooling of the total number of deaths showed an OR of 0.26 with ICS compared to placebo (95% CI 0.05 to 1.28; 1308 participants) (Comparison 2.8).

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Exacerbations

We pooled results for number of participants with at least one exacerbation for five medium-term studies (Paggiaro 1998; Laptseva 2002; Mahler 2002; Hanania 2003; GSK 2005 (FLTA3025)). One of these studies reported only moderate/severe exacerbations (Laptseva 2002) and the remaining four studies analysed all severities of exacerbations. The pooled OR for having at least one exacerbation during the study period was 0.90 for ICS compared to placebo (95% CI 0.75 to 1.08) (Comparison 2.9). Change in number of exacerbations was reported in several studies (Bourbeau 1998; Senderovitz 1999; Hattotuwa 2002) although not in sufficient detail to pool.

Quality of life and symptoms

Quality of life improved significantly within ICS, as measured by the SGRQ total and activity scores (Yildiz 2004) and symptoms score (John 2005), and by the Chronic Respiratory Questionnaire (Mahler 2002; Hanania 2003). There were no changes in health-related quality of life as measured by the Chronic Respiratory Questionnaire in one study (Bourbeau 1998).

Results of symptom scores were reported in several medium-term studies, but numerical data were generally not given in sufficient detail to pool. Cough improved in two studies (Paggiaro 1998; Hattotuwa 2002). Dyspnoea improved in one study (Mahler 2002) and was unchanged in three studies (Paggiaro 1998; Hattotuwa 2002; Hanania 2003). Sputum symptom score improved in two studies (Paggiaro 1998; Hattotuwa 2002) whereas chronic bronchitis symptoms were unchanged in two studies (Mahler 2002; Hanania 2003). Symptoms in general did not change in two studies (Bourbeau 1998; Senderovitz 1999).

Use of rescue bronchodilators

Rescue bronchodilator usage was reduced with ICS in two studies (Hattotuwa 2002; Mahler 2002) but not in the study by Tashkin 2008.

Exercise capacity

There was significant heterogeneity in change in six-minute walk distance between the two medium-term studies that measured this outcome (Bourbeau 1998; Paggiaro 1998). When these data were pooled, there was no statistically significant difference found with ICS compared to placebo (MD -4 metres, 95% CI -50 to 42) (Analysis 2.11).

Short-term studies (up to two months)

Cross-over studies

Two-week studies: Robertson et al studied 83 COPD participants in a cross-over study of BDP 1500 µg/day versus placebo, and also versus oral prednisolone for two weeks (Robertson 1986). Eighteen per cent of participants (15/83) showed an increase of at least 20% in FEV_1, FVC or PEFR over placebo or baseline when taking BDP. In a similar study design, Weir et al studied 127 participants using BDP 1500 µg/day versus placebo (and also a prednisolone arm) for two weeks (Weir 1990a). A few participants had bronchodilator reversibility, and some were non-smokers. Twenty-four per cent (8/34) of participants in the first of the cross-over periods showed at least 20% increased in FEV_1, FVC or PEFR from baseline. The effect of BDP on PEFR was still increasing at 14 days, and when withdrawn, the BDP effect was sustained above baseline for at least 14 days (Weir 1990b). Ferreira et al used BDP 1000 µg/day versus placebo in a two-week cross-over study of 20 participants (Ferreira 2001). There was no significant difference in FEV_1, FVC, bronchodilator response or diffusion capacity (DLCO) with BDP. In a study reported in abstract form, Ferreira et al studied 40 participants with FP 1000 µg/day versus placebo, and observed no significant differences in FEV_1, quality of life (Chronic Respiratory Questionnaire (CRQ)) or six-minute walk test (Ferreira 2003). Guenette et al studied 17 patients using FP 1000 µg/day versus placebo for two weeks, showing improvements in FEV_1 and reductions in lung volumes, as well as increased exercise endurance (Guenette 2011).

Four-week studies: Nishimura et al performed a cross-over study of BDP 3000 µg/day versus placebo for four weeks in 34 participants (Nishimura 1999). Overall, BDP significantly increased FEV_1, FVC and PEFR over placebo. BDP also improved scores of daily symptoms, wheeze and dyspnoea. Culpitt et al studied 13 participants with FP 1000 µg/day versus placebo in a four-week cross-over study (Culpitt 1999). There was no significant difference between FP and placebo in terms of FEV_1, PEFR, dyspnoea score, cough, sputum production or colour, or days free of relief medication. Brightling et al studied the effect of 400 µg/day of inhaled MF on 49 participants. There was no significant difference in FEV_1 between MF and placebo over six weeks (Brightling 2005).

Parallel studies

Two-week studies: in a study designed to test the effect of FP on systemic inflammation, Sin et al firstly withdrew participants from ICS then used FP 1000 µg/day versus placebo for two weeks, before continuing open-label FP (Sin 2004). Pre-bronchodilator FEV_1 did not change significantly in the first two weeks, although the authors noted that the study was not primarily designed for this.

Four-week studies: in a biomarker study, Sin et al studied FP 1000 µg/day versus placebo in 132 patients, as well as a salmeterol/fluticasone arm (Sin 2008). FP improved health status but not FEV_1.

Six-week studies: Thompson et al (Thompson 1992) studied BDP 2000 µg/day versus placebo for six weeks in 30 participants, and found that BDP increased FEV_1 by 10%, compared to 3% with placebo, although there was no change in rescue bronchodilator usage.

Eight-week studies: Llewellyn-Jones et al (Llewellyn-Jones 1996) found no significant difference in spirometry or PEFR, when using FP 1500 µg/day versus placebo for eight weeks.

Pooled results

The short-term studies focused mainly on lung function as an outcome. Pooling of lung function data was not possible, due to different spirometric outcomes measured or missing data. Taken together, these short-term studies of up to two months ICS in non-reversible COPD participants were generally of small sample size. The high dose of ICS used in these studies improved FEV_1 over the short term in a proportion of participants in some studies (Robertson 1986; Weir 1990a; Thompson 1992; Nishimura 1999; Guenette 2011) but there was no significant difference found in other studies (Llewellyn-Jones 1996; Culpitt 1999; Ferreira 2001; Ferreira 2003; Sin 2004; Brightling 2005). Symptoms or health status were generally not measured in these short-term studies; in the studies that did, symptoms or health status were improved

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(Nishimura 1999; Sin 2008) or unchanged (Culpitt 1999; Ferreira 2003).

Studies in people with COPD with bronchial hyperresponsiveness or bronchodilator reversibility

Long-term studies (longer than six months)

Kerstjens et al used BDP 800 µg/day, ipratropium, terbutaline or placebo for 30 months in 274 participants with obstructive airways disease (asthma, asthmatic bronchitis, COPD or undefined diagnosis) (Kerstjens 1992). The COPD subgroup data were analysed in the meta-analysis by van Grunsven et al (van Grunsven 1999). Data were included from the subgroup of 12 COPD participants (with BHR) who had BDP versus placebo in the Kerstjens study, who met criteria of absence of acute bronchodilator reversibility and other criteria (see 'Discussion').

The Detection, Intervention and Monitoring of COPD and Asthma (DIMCA) trial by van Grunsven et al studied 48 participants with COPD, of whom 27% had BHR (van Grunsven 2003). Participants received FP 500 µg/day or placebo for two years. In the initial three months, there was a benefit in post-bronchodilator FEV_1 of 125 mL. From three months to two years, there were no statistically significant differences in FEV_1 decline, symptoms or exacerbations.

Medium-term studies (longer than two months and up to six months)

Cross-over studies

Three month studies: Boothman-Burrell et al studied 18 COPD participants with salbutamol reversibility of less than 25%, in a cross-over study of BDP 2000 µg/day for three months each treatment period (Boothman-Burrell 1997). No significant differences in lung function tests were observed with BDP versus placebo. Thompson et al studied 52 participants using FP 880 µg/day versus placebo in a three-month cross-over study (Thompson 2002). Sixteen out of 36 participants had bronchodilator reversibility. Pre-bronchodilator FEV_1 improved with FP, as did RV/TLC ratio. PaO_2 increased with FP but there was no change in $PaCO_2$ or pH in the arterial blood. A small improvement in dyspnoea was observed in the CRQ quality of life questionnaire. There was no significant difference in the rate of exacerbations or symptoms such as sputum, wheezing or cough (Thompson 2002).

Parallel studies

Six-month studies: in a study of FP 1000 µg/day versus placebo over six months in 23 COPD participants with BHR, Verhoeven et al found that FP prevented the decline in FEV_1 but had no effect on BHR or inflammatory cell indices on bronchial biopsy (Verhoeven 2002).

Short-term studies (up to two months)

Cross-over studies

Four-week studies: Loppow et al investigated FP 1000 µg/day versus placebo in a four-week cross-over study in 19 participants with chronic bronchitis (Loppow 2001). Fourteen out of the 19 participants had BHR. No significant differences were found in lung function between the two treatment groups.

Six-week studies: Weiner et al recruited 30 participants, of whom eight had bronchodilator reversibility. Participants were treated with BUD 800 µg/day or placebo in a six-week cross-over study (Weiner 1995). BUD increased FEV_1 by at least 20% in six out of eight participants with bronchodilator reversibility, whereas there was no significant increase in FEV_1 in participants without bronchodilator reversibility. Rescue bronchodilator usage decreased in those participants who had bronchodilator reversibility and who were taking BUD (Weiner 1995). Weiner et al replicated and extended the study in 168 participants, of whom 44 had bronchodilator reversibility (Weiner 1999). Six-week cross-over comparisons were BUD 800 µg/day versus placebo, then BUD 1600 µg/day versus BUD 800 µg/day, then oral prednisone 40 mg/day versus placebo. In the participants with bronchodilator reversibility, there was a significant increase in FEV_1 with BUD 800 µg/day, and a decrease in the use of rescue bronchodilators. The higher dose of BUD or prednisone use did not improve the response. Participants without bronchodilator reversibility had no response to any of the active treatments (Weiner 1999).

Eight-week studies: Wempe et al studied 10 COPD participants with BHR in a cross-over study of BUD 1600 µg/day versus placebo for eight weeks (Wempe 1992). Oral prednisolone was also included as a separate treatment arm. No change in FEV_1 or PC_{20} was found with BUD in this study.

Parallel studies

Six-week studies: Rutgers et al examined BUD 1600 µg/day versus placebo for six weeks in 44 moderate-severe COPD participants with BHR (Rutgers 1998). They found no significant differences in FEV_1, PC20 to methacholine or PC20 to adenosine-monophosphate with BUD compared to placebo.
Eight-week studies: Auffarth et al studied 23 COPD participants with BHR using BUD 1600 µg/day versus placebo for eight weeks in a parallel study (Auffarth 1991). BUD reduced dyspnoea, but there was no change in spirometry, PEFR, PC_{20} histamine or citric acid cough threshold when compared to placebo.

Pooled results

In these studies of COPD participants with bronchial hyperresponsiveness or bronchodilator reversibility, pooling was not possible due to the small number of studies and various outcomes measured. Even in this subgroup of COPD participants who could be expected to have a greater benefit from ICS, there was no major effect on lung function. Mortality and exacerbations were generally not reported. There were minor improvements in quality of life and symptoms in a few studies. In general, these studies did not measure use of rescue bronchodilators or exercise capacity.

Predictors of response

Long-term studies (longer than six months)

Response to BUD was not predicted by gender, smoking or bronchodilator reversibility (Szafranski 2003). In the Copenhagen study, no significant difference in FEV_1 decline was noted with gender, smoking status or baseline FEV_1 (using a threshold of 70% predicted), although the authors commented that the study was not primarily powered for these subgroup analyses (Vestbo 1999). In the EUROSCOP study, BUD had a more beneficial effect in those participants who had smoked less than the median of 36 pack-years (Pauwels 1999). No association with response was found with

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age, gender, baseline FEV_1, atopy or bronchodilator reversibility. In the ISOLDE study, the decline in FEV_1 with FP versus placebo was not affected by age, smoking status, gender or FEV_1 response to oral steroids (Burge 2000; Burge 2003a). Current smokers had a reduced response to oral steroids, compared to ex-smokers, in COPD participants screened for the ISOLDE study (Burge 2003a).

Medium-term studies (longer than two months and up to six months)

Senderovitz et al employed response to oral steroids as a predictor of response to ICS (Senderovitz 1999). However, there were too few oral steroid-reversible participants for analysis. In the remaining participants who were non-reversible to oral steroids, there was no significant response to BUD 800 µg/day. Bourbeau et al measured response to oral steroids in potential participants then studied only those who had no response to oral steroids (Bourbeau 1998). In these oral steroid non-responders, there was no significant difference in FEV_1 or other secondary measures with BUD 1600 µg/day versus placebo. Paggiaro et al found no baseline predictors of response to FP, except for history of COPD of greater than 10 years (Paggiaro 1998). Mahler et al found that bronchodilator reversibility was associated with slightly better improvements in FEV_1 and dyspnoea (Mahler 2002).

Short-term studies (up to two months)

Some participants responded to either BDP or prednisolone in the cross-over study by Robertson et al (Robertson 1986), and only a minority of participants responded to both. Weir et al similarly showed that there were some responders to either BDP or prednisolone, with some full or partial responders to each (Weir 1990a). The presence of bronchodilator reversibility did not predict the presence of response to BDP or prednisolone (Weir 1990a). Smoking history and the presence of emphysema had no influence on being a responder (Weir 1990b; Weir 1991). There was a weak correlation (r = 0.38) between peripheral eosinophilia and response to high dose BDP in the study by Nishimura et al, whereas there was no correlation with other factors such as bronchodilator reversibility, total serum IgE or smoking history (Nishimura 1999).

Bronchodilator reversibility was found to be a predictive factor for response to ICS in the study by Weiner et al (Weiner 1995). They found that 25% of non-reversible COPD participants increased their FEV_1 significantly with BUD, and this response rate increased to 75% if bronchodilator reversibility was present. These results were replicated in a later study by the same group (Weiner 1999). A moderate correlation (r = 0.53) was observed between FEV_1 response to FP and bronchodilator reversibility (Thompson 2002). However, some participants with a substantial response to FP had no bronchodilator reversibility, which therefore did not exclude the possibility of a spirometric response to FP. Brightling et al observed that higher sputum eosinophilia was associated with a greater mean change in post-bronchodilator FEV_1 with inhaled MF, although there was no fall in sputum eosinophil count with MF (Brightling 2005).

Biomarker studies

Biopsy studies

Hattotuwa et al studied the effect of FP 1000 µg/day versus placebo on bronchial inflammation in 37 participants (Hattotuwa 2002). At three months, FP reduced mast cell numbers in the subepithelium and reduced the CD8:CD4 ratio in the epithelium. There was some improvement in symptoms but lung function was unchanged. Reduction in mucosal mast cell numbers was also shown by transmission electron microscopy in biopsies from the same study (Gizycki 2002). There was no change in eosinophil numbers in the biopsies (Gizycki 2002). It is unclear how the reduction in mast cell numbers relates to changes in symptoms, although it has been postulated that mast cells may be involved in mucus hypersecretion, and that reduction of mast cell numbers could contribute to the short-term improvements that are seen initially with ICS (Gizycki 2002). FP also apparently increased the number of neutrophils in the biopsies (Gizycki 2002). In a study of FP 1000 µg/day versus placebo over six months in 23 COPD participants with BHR, Verhoeven et al found no effect on inflammatory cell indices on bronchial biopsy (Verhoeven 2002). There were also no detectable effects on reactive oxygen species production from inflammatory cells in the bronchoalveolar lavage (BAL) (Verhoeven 2000), although some reduction in arachidonic acid metabolites was observed (Verhoeven 2001). FP 1000 µg/day for three months did not significantly change counts of CD8+ lymphocytes or CD68+ macrophages in bronchial biopsies, compared to placebo (Bourbeau 2007). However, a biopsy study at 30 months of FP 1000 µg/day showed reductions in CD4+ and CD8+ lymphocytes, reduction in mast cells, increase in eosinophils and increase in intact bronchial epithelium, as well as reduced sputum neutrophils, macrophages and lymphocytes (Lapperre 2009).

Induced sputum

Llewellyn-Jones et al measured sputum markers of inflammation (Llewellyn-Jones 1996). FP reduced the chemotactic activity of the sputum sol phase, and increased the capacity of the sputum to inhibit neutrophil elastase. There were no significant differences in sputum/serum albumin ratio, sputum myeloperoxidase concentration or peripheral blood neutrophil function (Llewellyn-Jones 1996). Culpitt et al measured inflammatory indices in induced sputum in a cross-over study of FP 1000 µg/day for four weeks (Culpitt 1999). FP did not alter sputum total cell count, neutrophil count or eosinophil count. There were no changes in sputum IL-8, MMP-1, MMP-9, TIMP-1, SLPI or elastase activity (Culpitt 1999). The authors concluded that FP had no anti-inflammatory effect in stable COPD. Mirici et al performed a 12-week study of BUD 800 µg/day versus placebo in 50 participants (Mirici 2001). They showed an improvement in FEV_1 of 7.4% predicted with BUD, compared to 0.7% predicted in the placebo group ($P < 0.01$). There was an increase in sputum macrophages but no change in sputum neutrophils with BUD, compared to placebo (Mirici 2001). Brightling et al examined the short-term response to six weeks of inhaled MF 800 µg/day (Brightling 2005). There were no treatment associated changes in sputum characteristics including eosinophil counts, histamine, IL-8 and ECP.

Exhaled nitric oxide (NO)

In a cross-over study of 20 participants, Ferreira et al found that BDP 1000 µg/day for two weeks resulted in a fall in median exhaled nitric oxide concentration, compared to placebo (Ferreira 2001). There were no changes in hydrogen peroxide in the exhaled breath condensate or lung function. The authors suggested that exhaled nitric oxide could be useful in predicting which participants would have an FEV_1 response to ICS.

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Bronchoalveolar lavage (BAL)

Thompson et al performed bronchoscopy before and after six weeks of BDP or placebo in 30 participants with chronic bronchitis (Thompson 1992). In the BAL-, BDP reduced cellularity, decreased levels of albumin (indicating reduced epithelial permeability), and decreased levels of lactoferrin and lysozyme (indicating reduced airway epithelial secretion). These results suggested the BDP was having an anti-inflammatory effect in these participants with chronic bronchitis. Ozol et al studied the effect of BUD 800 µg/day versus placebo for six weeks on BAL IL-8 and cell counts (Ozol 2005). BUD treated participants were found to have a statistically significant effect on markers on BAL- neutrophil counts and IL-8. These findings did not correlate with reported symptoms as only borderline improvements in sputum production and lung function were reported.

Systemic inflammation

Sin et al studied systemic inflammation in 41 mild to moderate COPD participants (Sin 2004). Withdrawal of ICS from COPD participants resulted in an increase in C-reactive protein (CRP), a marker of systemic inflammation. Addition of FP 1000 µg/day for two weeks decreased CRP by 50%, and a further eight weeks of FP reduced the CRP to below the baseline levels. In another study, Sin et al found that FP 1000 µg daily did not significantly effect the generalised biomarkers of C-reactive protein and IL-6, but did significantly reduce the lung-specific biomarker, surfactant protein D (Sin 2008). John et al studied three months treatment with HFA-BDP 800 µg/day, compared to placebo, in 11 participants. The HFA-BDP did not alter cytokine production from peripheral blood mononuclear cells (no change in IL-10, IFN- , GM-CSF and MIP-1) (John 2005). A systematic review has been performed for changes in sputum cell counts with ICS (Gan 2005) (see 'Discussion').

Side effects

Local steroid side effects

Long-term studies (longer than six months)

Pooling of available data in the long-term studies showed an increased risk of oropharyngeal candidiasis with ICS (OR 2.65, 95% CI 2.03 to 3.46, 5586 participants) (Analysis 1.15). For participants randomised to less than 1000 µg/day BDP equivalent this gave a number needed to treat to harm NNT(h) of 37. In studies assessing more than 1000 µg/day BDP equivalent, there was some variation in baseline risk. In participants from the control group of Burge 2000 risk was around 7%, and NNT(h) for participants randomised to steroid was 13 (95% CI 7 to 34), whereas in Calverley 2003a the control group event rate was 1.4%, giving a NNT(h) of 57 (95% CI 29 to 156). In Calverley 2008, the event rate was 11% amongst those randomised to ICS giving a NNT(h) of 13. There was also an increased risk of hoarseness or dysphonia (OR 1.95, 95% CI 1.41 to 2.70, 3267 participants) (Comparison 1.16). There was minimal heterogeneity, implying a consistent effect across the studies.

Medium-term studies (longer than two months and up to six months)

Pooling of the medium-term studies showed an increased risk of oropharyngeal candidiasis (OR 5.59, 95% CI 3.58 to 8.74, 2109 participants) (Comparison 2.18). Similarly there was an increase in hoarseness or dysphonia (OR 4.21, 95% CI 2.17 to 8.17, 1520 participants) (Comparison 2.19). There was a milder increase in throat irritation (OR 1.61, 95% CI 1.09 to 2.37, 1572 participants), although there was some heterogeneity between studies (Comparison 2.17).

Short-term studies (up to two months)

Hoarseness and sore throat were more common with very high-dose BDP (3000 µg/day) over four weeks (Nishimura 1999). FP 880 µg/day increased the risk of hoarseness (Thompson 2002).

Bone turnover and fractures

Long-term studies (longer than six months)

In the EUROSCOP study, there was no significant increased risk of vertebral fractures or osteoporosis in the participants treated with BUD (Pauwels 1999; Johnell 2002). In the ISOLDE study, there was no significant increase in the rate of fractures of any type (Burge 2003a). In the LHS II, a significant reduction in bone mineral density in the lumbar spine and femoral neck was measured in the group taking TAA, compared to placebo (LHS 2000; Scanlon 2004). In the TORCH study, there was no statistically significant difference in rate of fractures between FP and placebo over three years, and in a sub-study there was no statistically significant difference in bone mineral density (Calverley 2007). Pooling of available data on fractures from studies of a duration of one year or longer found no increase in the risk of fractures (OR 1.00, 95% CI 0.75 to 1.32, 5226 participants) (Comparison 1.21).

Short-term studies (up to two months)

Very high-dose BDP (3000 µg/day) reduced serum osteocalcin, compared to placebo (Nishimura 1999).

Cortisol

Long-term studies (longer than six months)

Serum cortisol did not differ at the end of two years of therapy with BUD 1600 µg/day versus placebo (Renkema 1996). The number of participants whose serum cortisol changed from normal to below normal did not differ between FP 1000 µg/day versus placebo (Calverley 2003a). In the ISOLDE study, there was a small decrease in mean serum cortisol with FP, compared to placebo (Burge 2003a). In the Lung Health Study II, TAA 1200 µg/day over three years did not significantly suppress baseline cortisol levels function or diminish adrenal responsiveness to cosyntropin stimulation (Eichenhorn 2003).

Medium-term studies (longer than two months and up to six months)

Serum cortisol was lower with six months of FP 1000 µg/day compared to placebo (Paggiaro 1998).

Short-term studies (up to two months)

The use of very high-dose BDP (3000 µg/day) over four weeks reduced serum cortisol levels in the study by Nishimura et al, but serum cortisol also decreased during the placebo period (Nishimura 1999). FP 880 µg/day over three months reduced pre- and post- adrenocorticotropic hormone (ACTH) cortisol levels, but there was no significant difference in the number who passed the ACTH stimulation test (Thompson 2002).

Pneumonia

In the long-term studies (longer than six months), the rate of pneumonia was increased in the ICS group compared to placebo, in six studies that reported pneumonia as an adverse event (OR

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1.56, 95% CI 1.30 to 1.86, 6235 participants) (Comparison 1.25). The statistically significant association was in the studies using ICS > 1000 µg BDP equivalent/day, whereas there was no statistically significant association in the ICS < 1000 µg BDP equivalent/day group.

Other effects

Skin bruising was increased with BUD in the EUROSCOP study (Pauwels 1999) and there were trends to increased skin bruising in other long-term studies (Burge 2000; LHS 2000; Calverley 2003a; Calverley 2008). Overall, the pooled OR for skin bruising with ICS was 1.63 (95% CI 1.31 to 2.03, 5073 participants). In the LHS, there was no overall difference in bruising or cataracts with TAA (LHS 2000). However, Tashkin et al, as part of the LHS II, found that amongst those participants who were adherent to ICS, a significantly higher proportion of participants reported easy bruising and slow healing of cuts or sores (LHS 2000). There was no increase in the rate of cataract formation (Burge 2003a; Calverley 2007).

DISCUSSION

This systematic review of inhaled corticosteroids (ICS) for chronic obstructive pulmonary disease (COPD) has analysed the following outcomes:

1. **Lung function**: Long-term use of ICS (more than six months) did not consistently reduce the rate of decline in forced expiratory volume in one second (FEV_1) in COPD patients (generic inverse variance analysis: mean difference (MD) 5.80 mL/year with ICS, 95% confidence interval (CI) -0.28 to 11.88, 2333 participants; pooled means analysis: 6.88 mL/year, 95% CI 1.80 to 11.96, 4823 participants).
2. **Mortality**: Long-term use of ICS had no statistically significant effect on mortality in COPD patients (odds ratio (OR) 0.98, 95% CI 0.83 to 1.16, 8390 participants).
3. **Exacerbations**: Long-term use of ICS reduced the mean rate of exacerbations in those studies where pooling of data was possible (generic inverse variance analysis: MD -0.26 exacerbations per patient per year, 95% CI -0.37 to -0.14, 2586 participants; pooled means analysis: MD -0.19 exacerbations per patient per year, 95% CI -0.30 to -0.08, 2253 participants).
4. **Quality of life and symptoms**: ICS slowed the rate of decline in quality of life, as measured by the St George's Respiratory Questionnaire (SGRQ) (MD -1.22 units/year, 95% CI -1.83 to -0.60, 2507 participants).
5. **Rescue bronchodilator use**: There was a reduction in rescue bronchodilator use in some medium-term studies.
6. **Exercise capacity**: This outcome was generally not measured.
7. **Biomarkers**: The relatively few studies that measured airway biomarkers showed a mixed response to ICS, with only some studies demonstrating an anti-inflammatory effect of ICS.
8. **Predictors of response**: Response to ICS was not predicted by oral steroid response, bronchodilator reversibility or bronchial hyper-responsiveness in COPD patients.
9. **Side effects**: ICS increased the risk of oropharyngeal candidiasis (OR 2.65, 95% CI 2.03 to 3.46, 5656 participants) and hoarseness. The few long-term studies that measured bone effects showed generally showed no major effect on fractures and bone mineral density over three years. In long-term studies that reported pneumonia as an adverse event, the rate of pneumonia was increased in the ICS group (OR 1.56, 95% CI 1.30 to 1.86, 6235 participants).

Lung function

Change in lung function was the primary outcome of the majority of long-term studies; hence, this was the a priori primary outcome of this systematic review. The question of effect of ICS on progression of airflow limitation has been addressed in a number of systematic reviews. The first systematic review was performed by van Grunsven et al (van Grunsven 1999). This meta-analysis combined data from two-year studies by Renkema et al (Renkema 1996) and Derenne (Derenne 1995), and a subgroup of the study by Kerstjens et al (Kerstjens 1992). They included individual patient data from these studies, and applied stricter criteria for COPD, consisting of pulmonary symptoms compatible with COPD, age 40 and over, persisting airflow obstruction post-bronchodilator, lack of reversibility to bronchodilator, and presence of smoking history. From the two-year Renkema et al study of 39 patients having budesonide (BUD) 1600 µg/day versus placebo (Renkema 1996), 30 were eligible for the meta-analysis. From the 30-month Kerstjens et al study of 51 COPD patients with bronchial hyper-responsiveness (BHR) having 800 µg/day versus placebo (or ipratropium, which was counted as "placebo") (Kerstjens 1992), 15 were eligible. The previously unpublished details of the study by Derenne 1995 were reported in the meta-analysis. Beclomethasone dipropionate (BDP) 1500 µg/day versus placebo was assessed over two years in 194 patients with moderate to severe COPD. Of these patients, 152 were eligible. Overall, the meta-analysis of these three studies found no benefit for change in post-bronchodilator FEV_1 with ICS, although there was a small benefit for change in pre-bronchodilator FEV_1 (van Grunsven 1999). The benefit was significant for higher doses of ICS; however, there were few patients receiving the lower dose. A review by Riancho 2002, published in the Spanish language, pooled short-term studies and found a small increase of 96 mL FEV_1 over one to six months. They observed that there was a small difference in FEV_1 of 51 mL in favour of ICS after one to three years of continued treatment. They concluded that ICS were probably not of benefit in patients with non-asthmatic COPD. In a systematic review of studies published up to 2001, Alsaeedi et al (Alsaeedi 2002) were unable to pool data for decline in FEV_1 due to lack of standard deviations for some of the studies.

Highland et al (Highland 2003) reviewed the long-term effects on FEV_1 in studies published up to 2002. These reviewers pooled data for rate of decline in FEV_1 for six long-term studies, and found a non-statistically significant difference of 5.0 mL/year with ICS (P = 0.11; 3571 participants). They concluded that there was no effect of ICS on long-term decline in FEV_1. The Highland et al meta-analysis was subsequently corrected by the authors, giving a MD of 5.31 mL/year (95% CI -0.64 to 11.2) (P = 0.08) (erratum in Ann Intern Med 2003;139(10):873). The accompanying editorial suggested that heterogeneity in inflammatory responses may explain some of the discordance between short-term clinical and long-term FEV_1 responses (Epstein 2003). In a similar analysis, Sutherland et al (Sutherland 2003) pooled data for rate of decline in FEV_1 for long-term studies published up to early 2003. In contrast to the Highland et al meta-analysis, the Sutherland et al meta-analysis showed that ICS reduced the rate of FEV_1 decline by 7.7 mL/year (P = 0.02; 3715 participants), and the effect was greater for higher doses

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of ICS. They concluded that ICS may potentially have important long-term effects in COPD. The accompanying editorial (Burge 2003b) elucidated the possible differences between the meta-analyses of Highland et al and Sutherland et al. With hypothetical adjustments to achieve more concordance in the data, the editorial by Burge and Lewis (Burge 2003b) showed that the Highland et al effect size would have been 5.5 mL/year (P = 0.07), compared to the Sutherland et al effect size of 7.7 mL/ year (P = 0.02). They pointed out that these mean effect sizes and P values were not too dissimilar. In our meta-analysis, the effect size of 5.8 mL/ year using the generic inverse variance analysis was between the two effect sizes found by Highland et al and Sutherland et al, as was our P value of 0.06 for this analysis. The main factors that explain the small differences between these effect sizes include (I) interpretation of numerical data, i.e. whether the direction of improvement in the Vestbo et al study (Vestbo 1999) was positive or negative (Burge 2003b), (ii) inclusion/exclusion of the EUROSCOP study which presented median values (Pauwels 1999), (iii) inclusion/exclusion of the van Grunsven et al meta-analysis, and (iv) calculation of missing standard deviations.

In the Inhaled Steroids Effect Evaluation in COPD (ISEEC) study, Soriano et al (Soriano 2007) pooled data from seven randomised controlled trials of ICS (3911 participants) versus placebo lasting ≥ 12 months in patients with moderate to severe COPD. Studies included were LHS-2, CCLS (Vestbo 1999), ISOLDE (Burge 2000), EUROSCOP (Pauwels 1999), TRISTAN (Calverley 2003a), Szafranski 2003 and Calverley 2003b. These authors found that in the first six months, ICS was associated with a significant mean increase in FEV_1 (mean change in FEV_1 2.42%, SE 0.19%, P < 0.01), and was more effective in ex-smokers (compared to current smokers) and women. However, for use of ICS in studies longer than six months, their systematic review found that ICS did not significantly improve FEV_1 decline (mean change in FEV_1 -0.01%, standard error (SE) 0.09%, P = 0.86).

In our updated systematic review, we pooled data for rate of FEV_1 decline in the long-term studies (> six months duration) using two statistical approaches, depending on reporting of data in the studies. The generic inverse variance analysis did not show a statistically significant difference in rate of FEV_1 decline calculated from baseline to study completion; however, the pooled means analysis of 4781 participants, which included the large TORCH study (Calverley 2007; Celli 2008), found a relatively small but statistically significant difference of 6.88 mL/year benefit, albeit with a wide confidence interval. In some of the medium-term studies (greater than two months and up to six months), there were small improvements in pre- and post-bronchodilator FEV_1 in favour of ICS.

Whether objective physiological measures are the best outcomes in COPD studies is still contentious. Furthermore, even if physiology is the optimal outcome, other measures such as inspiratory capacity may correlate better with subjective outcomes, compared to FEV_1. However, FEV_1 has been shown to be a prognostic factor in COPD, and remains the defining criterion for the diagnosis and severity of COPD. Hence lung function was the primary outcome of interest in the majority of the long-term trials. The clinically important difference in change in rates of FEV_1 decline is not yet clearly known. As discussed by others, a difference in rate of decline in FEV_1 of magnitude ~6 mL/year could be considered clinically unimportant when compared to a current smoker rate of 60 mL/year, and clinically important when compared to a non-smoker rate of 30 mL/ year (Burge 2003b). Another issue is that excessive dropouts from the placebo group who have rapid decline may mean that the effect size of active treatment is underestimated, because the remaining participants in the placebo group have less rapid decline (Calverley 2003d), although attrition bias could affect decline in the opposite direction (Suissa 2008). It has also been debated as to whether the small improvement on FEV_1 observed in some short and medium-term studies is of clinical importance (Burge 2003b).

Taking these considerations into account, our systematic review has found that use of ICS alone in COPD patients results in a small, initial improvement in FEV_1, and then no consistent improvement in the long-term rate of decline in FEV_1, although long-term use of ICS > 1000 µg BDP daily equivalent may be associated with a small improvement in the rate of decline in post-bronchodilator FEV_1.

Mortality

Mortality is a major health outcome in COPD. Of the long-term studies, only Calverley 2007 was designed to study the effect of ICS on mortality as a primary outcome; hence, we analysed mortality as a secondary outcome. In this current review, the available mortality data from nine long-term studies involving long-term use of ICS had no statistically significant effect on mortality (OR 0.98 for mortality, 95% CI 0.83 to 1.16, P = 0.84, 8390 participants). The data from five medium-term studies also showed no statistically significant effect on mortality.

Observational studies have found reduced mortality with the use of ICS in COPD patients (Sin 2001; Sin 2003a; Soriano 2003; Mapel 2006), including reduction in cardiovascular deaths (Macie 2006). Various epidemiological issues arising from these observational studies have been discussed, including immortal time bias, which is the issue of unaccounted-for survival time in the 'treatment' group before they actually received treatment (Suissa 2003; Suissa 2004).

The effect of ICS on mortality in COPD patients has been addressed by recent meta-analyses. Alsaeedi et al (Alsaeedi 2002) found a non-significant relative risk of 0.84 (95% CI 0.60 to 1.18, 3473 participants) in five long-term studies published up to 2001. The systematic review by Gartlehner et al of 12 studies published up to early 2005 observed a non-significant relative risk of 0.81 (95% CI 0.60 to 1.08, 4370 participants) (Gartlehner 2006).

The systematic review by Sin et al, using individual patient data from seven studies up to 2005 involving 5085 patients (Sin 2005), found a mortality benefit with ICS in COPD. The adjusted hazard ratio for all-cause mortality from their review was 0.73 (95% CI 0.57 to 0.99, P = 0.03, 5085 participants). Their review found that the mortality benefit with ICS was stronger in specific subgroups: females, former smokers and patients with baseline post-bronchodilator FEV_1 less than 60% predicted. The systematic review of Sin et al had the methodological strength of access to individual patient data, in order to adjust for age, sex, baseline lung function, smoking status and body mass index (Wedzicha 2005). Hence they were able to present adjusted hazard ratios across the individual trials. As discussed in the editorial accompanying the Sin et al meta-analysis (Wedzicha 2005), the effect sizes of ICS in various meta-analyses appeared to be similar across several major outcomes, e.g. ~25% reduction in exacerbations, 25%

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improvement in rate of decline of FEV_1 (compared to the non-smoker rate) and 27% reduction in mortality from the Sin et al review.

Our current review has found no significant difference in mortality rate with the use of ICS as a mono-component versus placebo. This lack of effect was found both in the long-term studies published prior to the TORCH study, and in all long-term studies pooled including TORCH. The TORCH study itself, which was the largest of the long-term studies, found no mortality benefit with fluticasone propionate (FP) as a mono-component, although the combination of salmeterol/fluticasone potentially reduced mortality (Calverley 2007). Limitations of pooling data from the long-term studies have been discussed in detail by others, including the use of intention-to-treat analysis versus completed participants in some studies, different run-in protocols and differential effect of dropouts (Wedzicha 2005). Even given these limitations, the pooled data indicate no statistically significant mortality benefit for ICS given as a mono-component. The meta-analysis by Drummond 2008 of 11 studies (14,426 participants), including studies of combination inhaler versus long-acting $beta_2$-agonist (LABA), found no difference in mortality rate at one year.

Exacerbations

Acute exacerbations are an important cause of morbidity and mortality in COPD patients (Donaldson 2006). In our current review, data were available for pooling in some of the long-term and medium-term studies. Where pooling of data was possible in the long-term studies, there was a statistically significant benefit of ICS in reducing the mean rate of exacerbations (generic inverse variance analysis: MD -0.26 exacerbations per patient per year, $P < 0.0001$, 2586 participants; pooled means analysis: MD -0.19 exacerbations per patient per year, 95% CI -0.30 to -0.08, 2253 participants).

In a systematic review of studies up to 2001, Alsaeedi et al pooled the total COPD exacerbation rates, by calculating the frequency of COPD exacerbations per patient-month of treatment (Alsaeedi 2002). Their review found a significant benefit of ICS for reducing exacerbations (risk ratio (RR) 0.70, 95% CI 0.58 to 0.84, 2615 participants). In the systematic review of studies up to early 2005, Gartlehner et al found a reduction in the rate of COPD exacerbations with ICS (RR 0.67, 95% CI 0.59 to 0.77, 4300 participants) (Gartlehner 2006). This effect size was based on data pooled from both medium and long-term studies. In their review, the benefit was mainly in the moderate to severe COPD subgroup. Variations in the approach to analysis are seen in the systematic reviews of Alsaeedi et al and Gartlehner et al, compared to our review. Their data were primarily analysed in terms of relative risk, rather than differences in mean rates of exacerbations. Furthermore, there were some minor differences with our review in terms of the selection of studies for inclusion and the particular exacerbation outcome extracted. The meta-analysis by Agarwal 2010 found a small but statistically significant reduction in the risk of exacerbations (RR 0.82, 95% CI 0.73 to 0.92, 8164 participants), when analysing risk of exacerbations, as opposed to exacerbations per patient per year. This was similar to our result of OR 0.83 when analysing risk of exacerbations (Comparison 1.8).

Methodological issues have recently been discussed in detail in relation to analysis of exacerbation rates. It has been suggested that accounting for the length of follow-up time of each participant (weighted approach) is a potentially less biased method of analysis than not accounting for this (unweighted approach) (Suissa 2006). To explore this, we stratified the long-term studies by whether they used the weighted or unweighted approach (Comparison 1.7). In both approaches, a statistically significant reduction in exacerbations was observed. Variation in the definition of exacerbations and in study design (for example, run-in periods) may also account for differences between study outcomes in relation to exacerbation rates (Scott 2006). Cohort studies have observed populations of frequent and non-frequent exacerbators (Vestbo 2011). The presence of these distinct patient groups may lead to a bimodal, non-normal distribution of exacerbation rates, making analysis more complex (Scott 2006). Therefore, it may be that ICS can reduce the number of exacerbations, particularly in frequent exacerbators (that is, frequent exacerbators have a reduction in the number of exacerbations) yet may not reduce the percentage of patients with one or more exacerbations (i.e. the frequent exacerbators do not become non-frequent exacerbators). Other methodological issues raised included the discontinuation of ICS in patients who are already taking these prior to commencement of a trial, and lack of complete follow-up of exacerbations on an intention-to-treat basis in those participants who have withdrawn from the study (Suissa 2008a), which could both overestimate the observed benefits of ICS.

Even taking into account these issues, and also the lack of available data to pool in some of the medium and long-term studies, our systematic review has observed a statistically significant reduction in the mean exacerbation rate per year with ICS. The magnitude of the effect is relatively small yet potentially important, given that frequent exacerbations worsen lung function decline (Kanner 2001; Donaldson 2002; Vestbo 2011) and reduce quality of life.

Quality of life and symptoms

Improving patient-centred, subjective outcomes is an important goal in the management of COPD. This systematic review found that, in those long-term studies which measured quality of life and where data could be pooled, ICS slowed the rate of decline in quality of life, when measured with the SGRQ. The magnitude of this benefit was relatively small (MD -1.22 units/year), compared to the minimum clinically significant difference of 4 units with the SGRQ. The effect on quality of life appeared linear, based on graphical analysis of change in quality of life scores in each study (data not shown). Medium-term use of ICS tended to improve quality of life, although pooling of data was not possible. Some medium-term studies showed that an improvement in respiratory symptoms, but not all studies were able to demonstrate this. In the systematic review by Gartlehner et al, quality of life was examined qualitatively and was not pooled due to heterogeneity (Gartlehner 2006). Overall our review showed a small yet statistically significant benefit for quality of life using ICS. It is not clear whether this benefit is related to other benefits such as reduced frequency of exacerbations.

Rescue bronchodilator use

There was reduction of rescue bronchodilator use found in some medium-term studies, although the data could not be pooled. Rescue bronchodilator use was generally not measured in the long-term studies.

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Exercise capacity

This outcome measure was only infrequently measured, and overall no significant difference was found with ICS.

Biomarkers

There have been relatively few randomised, controlled trials of the effects of inhaled steroid on biomarkers in COPD. Due to the heterogeneity of outcomes used, we performed a narrative review of these biomarker studies. Some studies observed reductions in airway neutrophil counts and other anti-inflammatory effects such as reduced exhaled nitric oxide. Other studies found no significant difference in inflammatory cells in the airways (as measured in biopsies, induced sputum and BAL fluid). Overall, this qualitative review showed a mixed response of airway biomarkers to ICS in COPD patients. This could partially be explained by the relative steroid resistance due to reduced histone deacetylase activity in COPD lungs (Barnes 2004; Ito 2005).

A systematic review was performed by Gan et al of the effects of ICS on sputum cell counts (Gan 2005). Gan et al found that longer treatment duration (more than six weeks) or higher dose (> 60 mg cumulative dose) resulted in greater reductions in sputum total cell count, neutrophil count and lymphocyte count, with no significant differences in macrophages or eosinophil counts (Gan 2005). Due to differences in reporting study outcomes, they analysed standardised mean differences. Some of their nine included studies were double-blinded and other studies were single-blinded or open-label studies, which differs from our review in that only double-blinded studies were included in our review. Another report has suggested that ICS may have an important effect on systemic inflammation in COPD (Man 2005a).

Predictors of response

Predicting the response to ICS in COPD patients is a clinically useful goal, in order to individualise treatment. Clinical indicators such as oral steroid responsiveness or current smoking did not adequately predict responders to ICS. Some studies included COPD patients with bronchodilator reversibility or bronchial hyper-responsiveness, although the number of studies and their sample sizes were small. The presence of bronchodilator reversibility and bronchial hyper-responsiveness in COPD generally did not predict responsiveness to ICS. Therefore, the challenge remains to identify clinical or biological factors that predict those COPD patients who are more likely to benefit from long term ICS.

Side effects

The safety aspects of ICS are important in the long term, especially in older COPD patients with co-morbidities. As expected, our review found an increased risk of local side effects such as oropharyngeal candidiasis. The systemic effects of prolonged use were less clear, with several studies showing no change in fracture rate or bone mineral density (Pauwels 1999; Johnell 2002; Burge 2003a; Calverley 2007), whereas one study using a smaller dose of ICS showed a reduction in bone mineral density (LHS 2000). The systematic review by Alsaeedi et al noted that there was an increase in oropharyngeal candidiasis and skin bruising, and variable effects on bone mineral density (Alsaeedi 2002). The systemic review by Gartlehner et al observed that there were variable results on bone mineral density and risk of fractures, including in some case-control studies (Gartlehner 2006). The meta-analysis by Loke 2011 pooled results from randomised controlled trials (RCTs) of ICS or combination inhalers, and observational studies, and found a small but statistically significant increase in risk of fractures with ICS use in COPD. Our review found no statistically significant increase in fracture risk in studies of ICS as a mono-component versus placebo for one year or longer.

In the long-term studies, the rate of pneumonia as an adverse event was increased in the ICS group, in the six studies that reported this outcome (OR 1.56, 95% CI 1.30 to 1.86, 6235 participants). The TORCH study observed a reduction in rate of exacerbations, but also an increase in self reported pneumonia in the adverse events and serious adverse events (Calverley 2007; Crim 2009), although radiological or microbiological confirmation was not required. In a meta-analysis using patient-level data and adjusting for clinical confounders, Sin et al found no increased risk of pneumonia at one year of budesonide (or budesonide/formoterol) use in COPD (adjusted hazard ratio 1.05, 95% CI 0.81 to 1.37, 7042 participants) (Sin 2009). In contrast, two meta-analysis found similar results to our pooled result of increased risk of pneumonia. The meta-analysis by Drummond 2008 of any ICS (including in combination inhalers) found an increase in risk of pneumonia (RR 1.34, 95% CI 1.03 to 1.75). Similarly the meta-analysis by Singh 2009 found an increased risk of pneumonia with any ICS use (including in combination inhalers) for at least 24 weeks in COPD, with RR 1.60 (95% CI 1.33 to 1.92), but no increase in pneumonia-related mortality or overall mortality.

The mechanisms for this potential increase in pneumonia are unclear. In the two-year INSPIRE study of salmeterol/fluticasone versus tiotropium, the number of *de novo* pneumonias not preceded by symptoms of exacerbations were similar between the two treatment groups (Calverley 2011). However, unresolved exacerbations preceding pneumonia were more common in the salmeterol/fluticasone-treated patients (32 exacerbations in 658 patients), compared to the tiotropium-treated group (seven exacerbations in 665 patients). Future studies should prospectively confirm the diagnosis of pneumonia using clinical and radiological evidence (Welte 2009). Until the risk of pneumonia is confirmed, clinicians should be vigilant to the development of pneumonia in COPD patients, particularly those with prolonged exacerbations.

Interpretation of results

In interpreting the results of this systematic review, a number of clinical and epidemiological issues should be considered. There was wide variability in study characteristics, including dose and duration of ICS, severity of COPD, inclusion criteria (e.g. current or ex-smokers, bronchial hyper-responsiveness, bronchodilator reversibility) and outcomes studied. Furthermore, results for outcomes were sometimes either missing or could not be pooled (e.g. non-parametric data; continuous versus categorical classification of similar outcomes such as change in FEV_1). Subgroup analysis, whilst potentially useful, was not possible due to lack of individual data. With the use of the generic inverse variance function, it was possible to pool data for some of the medium-term and long-term studies. Side effects were measured in most of the studies, although even longer studies would probably be required to determine the rates of adverse effects such as vertebral fractures and cataracts. The ICS only studies reviewed here should be interpreted in the light of the newer studies using combination inhalers of LABA/ICS, which may be more effective than ICS alone in COPD. Finally, participants who withdrew from

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the placebo arm of the long-term ICS studies may have been those patients who were deteriorating the most rapidly, which may underestimate the effect of active treatment (Calverley 2003d).

Conclusions

This systematic review has analysed all relevant published and unpublished RCTs of inhaled steroids used as a mono-component, in patients with stable COPD. Despite variability in study design, interventions and outcomes used, pooling of data was possible for important outcomes, particularly in the long-term studies. Inhaled steroids had a beneficial effect on frequency of COPD exacerbations and rate of decline of quality of life, whereas they did not appear to have consistent effects on lung function decline or mortality in COPD. Local side effects (oropharyngeal candidiasis and hoarseness) were increased, and the risk of pneumonia was possibly increased. Therefore clinicians and patients should balance the potential benefits of inhaled steroids in COPD (possible reduction in rate of lung function decline, reduced exacerbations, reduced rate of decline in quality of life) against the potential side effects (local oropharyngeal effects and increase in risk of pneumonia).

AUTHORS' CONCLUSIONS

Implications for practice

We are able to make several statements on the efficacy and safety of long-term use of inhaled steroids in people with COPD:

- Long-term use of inhaled steroids as a mono-component has not been shown to consistently reduce the rate of decline in FEV_1 in COPD patients.
- Long-term use of inhaled steroids as a mono-component does not significantly reduce mortality in COPD.
- Long-term use of inhaled steroids reduces the mean rate of COPD exacerbations per patient per year.
- Inhaled steroids slow the rate of decline in quality of life in COPD.
- No factors adequately predict response to inhaled steroids in COPD.
- Local side effects are increased with use of inhaled steroids in COPD patients, whereas the long-term effects may include increased risk of pneumonia.

Clinicians and patients should balance the potential benefits of inhaled steroids in COPD (possibly reduced rate of decline in FEV_1, reduced exacerbations, reduced rate of decline in quality of life) against the potential side effects (oropharyngeal candidiasis and hoarseness, and pneumonia).

Implications for research

This review has raised several questions which merit further research:

- Which COPD patients should be commenced on inhaled steroids?
- What are the clinical and biological factors that predict response to inhaled steroids in COPD patients?
- What is the dose-response for treatment effects of inhaled steroids in COPD patients?
- What are the long-term side effects of inhaled steroids in COPD patients, especially risk of pneumonia?
- What are the benefits of adding inhaled steroids to long-acting $beta_2$-agonists, anticholinergics and other anti-inflammatory agents such as roflumilast?
- What are the mechanisms for the variable response to inhaled steroids in COPD patients and what are the potential strategies for reversing steroid resistance?

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Auffarth 1991

Methods	Design: parallel-group Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: single-centre study, hospital outpatient clinic Number eligible: not stated Number enrolled: 24 Number in treatment group: 12 Number in control group: 12 Number of withdrawals (treatment/control): 2/1 Number completing trial (treatment/control): 10/11 Age range: 40 to 70 years Sex: 23 M, 1 F Ethnicity: not stated COPD diagnosis: FEV1 30% to 75% predicted, with bronchial hyper-responsiveness to histamine (defined in inclusion criteria) Severity of COPD: FEV1 52.5% predicted (BUD group), 54.1% predicted (placebo group) Inclusion criteria: smoking at least 1 cigarette a day for at least 5 years, reversibility in terms of the difference between FEV1 % predicted before and after 0.5 mg inhaled terbutaline of < 20%, PC20 to histamine < 16 mg/mL Exclusion criteria: positive skin prick test or specific IgE to house dust mite, total serum IgE >= 470 IU/mL, peripheral blood eosinophil count >= 0.2 x 10 E6/L, upper respiratory tract infection or oral corticosteroids in the 2 months prior Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 200 µg, 4 puffs, 2 times a day (1600 µg/d) Placebo 4 puffs, 2 times a day Nebuhaler 8 weeks
Outcomes	FEV1 Bronchodilator response

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Auffarth 1991 *(Continued)*

	PC20 histamine Citric acid threshold (cough) Morning peak expiratory flow rate Evening peak expiratory flow rate Symptoms of cough Symptoms of dyspnoea Sputum volume Number of rescue bronchodilator (ipratropium) inhalations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "allocated at random"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind design"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Boothman-Burrell 1997

Methods	Design: cross-over, 4 weeks washout Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: single-centre study, research clinic Number eligible: not stated Number enrolled: 22 Number in treatment group: 22 (cross-over study) Number in control group: 22 (cross-over study) Number of withdrawals (treatment/control): 4 (cross-over study) Number completing trial (treatment/control): 18 (cross-over study) Age range: > 40 years Sex: numbers not stated Ethnicity: not stated COPD diagnosis: FEV1 < 80% predicted, FEV1/FVC < 65% Severity of COPD: FEV1 52.4% predicted Inclusion criteria: smokers or ex-smokers of > 10 pack-years, reversibility to salbutamol < 25%. 5 patients had bronchodilator reversibility of 15% to 25%. 2 patients had PC20 methacholine < 16 mg/mL Exclusion criteria: childhood asthma, eczema, allergic rhinitis, other current respiratory disorder, taking oral prednisone, other major disease, major exacerbation in previous 2 months Baseline characteristics of treatment/control groups: cross-over study

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Boothman-Burrell 1997 *(Continued)*

Interventions	BDP 1000 µg, 2 times a day (2000 µg/d) Placebo 2 times a day Metered-dose inhaler 3 months each treatment period (cross-over)
Outcomes	Post-bronchodilator FEV1 Methacholine challenge Symptom scores (cough, dyspnoea, wheeze, sputum production) Early morning PEFR Adverse events Exacerbations
Notes	3 months each treatment period (cross-over) Oral steroid reversibility trial (prednisone 30 mg/day) for 10 days after each treatment or placebo period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 withdrawals (cross-over study)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Bourbeau 1998

Methods	Design: parallel-group Randomisation: yes, sealed envelopes, block of 4 patients Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: single-centre study, Canada, hospital outpatient clinic, home recordings Number eligible: 140 Number enrolled: 79 Number in treatment group: 39 Number in control group: 40 Number of withdrawals (treatment/control): 3/10 Number completing trial (treatment/control): 36/30 Age range: >= 40 years Sex: 62 M, 17 F Ethnicity: not stated

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Bourbeau 1998 *(Continued)*

	COPD diagnosis: pre-bronchodilator FEV1 < 65% predicted, FEV1/FVC < 0.65, post-bronchodilator FEV1 < 80% Severity of COPD: mean post-bronchodilator FEV1 43% predicted in intervention group, 43% predicted in placebo group Inclusion criteria: smokers or ex-smokers, regular treatment with at least one bronchodilator, non-response to oral steroid trial (prednisolone 40 mg 2 weeks, taper over 1 week) defined as increase in pre-bronchodilator FEV1 < 15% and < 200 mL compared to baseline or placebo Exclusion criteria: allergic asthma during childhood or adulthood, exacerbation in respiratory symptoms during 2 months prior to study, other active lung disease, diabetes, active peptic ulcer disease, uncontrolled high blood pressure, congestive heart failure, disease other than COPD that interferes with quality of life Baseline characteristics of treatment/control groups: more women and current smokers in placebo group
Interventions	BUD 800 µg, 2 times a day (1600 µg/d) Placebo 2 times a day Dry powder inhaler (Turbuhaler) 6 months
Outcomes	Change from baseline in pre-bronchodilator FEV1 Change from baseline in pre-bronchodilator FVC Change from baseline in post-bronchodilator FEV1 Change from baseline in post-bronchodilator FVC Change from baseline in 6-minute walk distance Change from baseline in 6-minute walk visual analogue score Quality of life questionnaire (CRQ) Morning PEFR Evening PEFR Shortness of breath score Cough score
Notes	Run-in phase (trial of oral steroids): oral placebo 2 weeks then prednisolone 40 mg 2 weeks, taper over 1 week. Oral steroid non-responders were enrolled in the RCT of budesonide versus placebo. Intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was carried out in blocks of 4 patients", "sealed envelopes"
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was carried out in blocks of 4 patients", "sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals: 3 from BUD group, 10 from placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported

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Bourbeau 2007

Methods	Design: parallel-group Randomisation: Yes. central computer-generated list of random numbers which was stratified by centre and which used a block size of 6 Blinding: double-blind Withdrawals: stated
Participants	Setting: 2 respiratory centres (Montreal Chest Institute and Hospital Laval, Canada) Number eligible: 62 Number enrolled: 60 Number in treatment groups: SFC 19, FP 20 Number in control group: 21 Number of withdrawals: SFC 0, FP 3, placebo 9 Number completing trial: SFC 19, FP 17, placebo 15 Mean age: SFC 62, FP 64, placebo 66 Sex (M/F): SFC 19/0, FP 15/5, placebo 17/4 Ethnicity: not stated COPD diagnosis: as stated below Severity of COPD: as stated below Inclusion criteria: age > 40 and (75 years; smoking history (> 10 pack-years); post-bronchodilator FEV1 > 25% of predicted value and FEV1/forced vital capacity (FVC) ≤ 0.70; no history of asthma, atopy (as assessed by an allergy skin prick test during screening) or any other active lung disease Exclusion criteria: home oxygen or with raised carbon dioxide tension (> 44 mm Hg), alpha1-antitrypsin deficiency, recent exacerbation (in the last 4 weeks), uncontrolled medical condition or hypersensitivity to inhaled corticosteroids and bronchodilators Baseline characteristics of treatment/control groups: no females and greater pack-year history smoking in SFC group
Interventions	4 weeks washout period from ICS and LABA. 12 weeks treatment with salmeterol xinafoate/fluticasone propionate 50/500 µg twice daily, fluticasone propionate 500 µg twice daily, or placebo twice daily
Outcomes	Primary: number of CD8+ T cells and CD68+ macrophages Secondary: number neutrophils and eosinophils, FEV1, CRQ score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computed generated randomisation"
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts stated, equal

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Bourbeau 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported

Brightling 2005

Methods	Design: cross-over, 4 week run-in, 4 weeks washout Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: single-centre study, respiratory outpatient clinic, Leicester Number eligible: 95 Number enrolled: 60 Number in treatment group: 30 Number in control group: 30 Number of withdrawals (treatment/control): 5/6 Number completing trial (treatment/control): 23/26 Age range: 66 to 68 years Sex: 35 M; 25 F Ethnicity: not stated COPD diagnosis: post-bronchodilator FEV1 of < 70% predicted and FEV1/FVC ratio of < 70%, no significant improvement in FEV1 after inhaled salbutamol Severity of COPD: Inclusion criteria: COPD Exclusion criteria: clinical diagnosis of asthma; history of childhood respiratory problems; variability in symptoms not associated with infections; a history of acute wheeze, breathlessness or deterioration associated with allergens; an exacerbation within 6 weeks of trial entry; taking regular oral corticosteroids Baseline characteristics of treatment/control groups: comparable
Interventions	Mometasone furoate 800 µg, 1 time a day (800 µg/day) Placebo
Outcomes	Change in post-bronchodilator FEV1 Total CRQ Sputum characteristics - eosinophils, neutrophils, macrophages, lymphocytes, histamine, IL8, ECP VAS scores for dyspnoea, cough, sputum production, wheeze
Notes	Intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias)	Low risk	Withdrawals: 2 MF, 1 placebo

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Brightling 2005 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	All outcomes reported

Burge 2000

Methods	Design: parallel-group Randomisation: yes, computer-generated, stratified by centre Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: multicentre study, UK, hospital outpatient clinics Number eligible: 990 Number enrolled: 751 Number in treatment group: 376 Number in control group: 375 Number of withdrawals (treatment/control): 164/200 Number completing trial (treatment/control): 212/175 Age range: 40 to 75 year Sex: 560 M, 191 F Ethnicity: not stated COPD diagnosis: post-bronchodilator FEV1 >= 0.8 L and < 85% predicted, FEV1/FVC < 70% Severity of COPD: mean post-bronchodilator FEV1 50.3% predicted in intervention group, 50.0% predicted in placebo group Inclusion criteria: current or former smokers Exclusion criteria: asthma, FEV1 increase > 10% predicted with 400 µg salbutamol, life expectancy < 5 years from concurrent diseases, use of beta-blockers Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1000 µg/day) Placebo 2 times a day Metered-dose inhaler (identical) and spacer device 3 years
Outcomes	Change in post-bronchodilator FEV1 over time Exacerbations Changes in health status (SGRQ) Withdrawals because of respiratory disease Morning serum cortisol Adverse events
Notes	Run-in phase: 8-week: withdrawal from oral or inhaled steroids

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer generated allocation schedule"
Allocation concealment (selection bias)	Unclear risk	Information not available

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Burge 2000 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals: 43% FP, 53% placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Calverley 2003a

Methods	Design: parallel-group Randomisation: yes, computer-generated Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient clinic Number eligible: 1974 Number enrolled: 1465 (all treatment arms) Number in treatment group: 374 FP arm Number in control group: 361 placebo arm Number of withdrawals (treatment/control): 108/140 Number completing trial (treatment/control): 266/221 Age range: mean 63 years Sex: 529 M, 206 F Ethnicity: not stated COPD diagnosis: pre-bronchodilator FEV1 25% to 70% predicted, acute bronchodilator reversibility < 10% predicted FEV1 with salbutamol, pre-bronchodilator FEV1/FVC ratio <= 70% Severity of COPD: mean FEV1 45% predicted FP, 44% predicted placebo Inclusion criteria: >= 10 pack-years smoking, chronic bronchitis, at least 1 episode of acute COPD symptom exacerbation per year in the previous 3 years, at least one exacerbation in the year immediately before trial entry that required treatment with oral steroids, antibiotics or both Exclusion criteria: respiratory disorders other than COPD; regular oxygen treatment; systemic steroids, high dose ICS or antibiotics in the 4 weeks prior Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1000 µg/d) Salmeterol/FP 50/500 µg, 2 times a day Salmeterol 50 µg, 2 times a day Placebo in identical inhaler Multidose dry powder inhaler (Diskus or Accuhaler) 1 year
Outcomes	Pre-bronchodilator FEV1, FVC Post-bronchodilator FEV1, FVC Peak flow Use of relief medication Symptoms score Night-time awakenings Exacerbations SGRQ Adverse events
Notes	Study of combined salmeterol and fluticasone, versus salmeterol, versus fluticasone, versus placebo.

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Calverley 2003a *(Continued)*

For this review, the comparison of fluticasone versus placebo was analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation schedule generated by the PACT program"
Allocation concealment (selection bias)	Low risk	Quote: "unaware of the allocated treatment"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 108 FP, 140 placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Calverley 2003b

Methods	Design: parallel-group Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient clinic Number eligible: not stated Number enrolled: 1141 (all treatment arms) Number in treatment group: 257 (BUD) Number in control group: 256 (placebo) Number of withdrawals (treatment/control): 102 BUD/106 placebo Number completing trial (treatment/control): 155 BUD/150 placebo Age range: mean 64 years BUD, mean 65 years placebo Sex: 74% M BUD, 75% M placebo Ethnicity: not stated COPD diagnosis: GOLD stages III and IV Severity of COPD: FEV1 36% predicted Inclusion criteria: GOLD defined COPD (stages III and IV); >= 40 years; COPD symptoms > 2 years; smoking history >= 10 pack-years; FEV1/VC <= 70% pre-BD; FEV1 <= 50% predicted; use of SABAs as reliever medication; >= 1 COPD exacerbation requiring OCS/antibx 2 to 12 months before 1st clinic visit Exclusion criteria: history of asthma/rhinitis before 40 years of age; any relevant cardiovascular disorders; exacerbation of COPD requiring medical intervention within 4 weeks of run-in/during run-in phase; non-allowed medications: O2 therapy; ICS (aside from study medication), disodium cromoglycate, leukotriene-antagonists, 5-LO inhibitors, BD (other than study medication and prn terbutaline 0.5 mg), antihistamines, medication containing ephedrine, ß-blocking agents Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 400 µg bd Formoterol 9 µg bd BUD 320 µg/formoterol 9 µg bd Placebo bd

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Calverley 2003b *(Continued)*

	Turbuhaler 12 months
Outcomes	Time to first exacerbation Change in post-bronchodilator FEV1 Number of exacerbations Time to and number of OCS-treated episodes PEFR am and pm Slow VC HRQL Symptoms Use of reliever medication Adverse effects
Notes	Study of combined budesonide and formoterol, versus budesonide, versus formoterol, versus placebo For this review, the comparison of budesonide versus placebo was analysed Run-in phase: all participants received 30 mg oral prednisolone bd and 2 x 4.5 mg formoterol bd (2 weeks)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 102 BUD, 106 placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Calverley 2003c

Methods	Design: parallel-group Randomisation: yes, method not stated Blinding: not stated (placebo-controlled) Withdrawals: not stated
Participants	Setting: multicentre study Number eligible: not stated (abstract) Number enrolled: 631 Number in treatment group: 318 Number in control group: 313 Number of withdrawals (treatment/control): not stated Number completing trial (treatment/control): not stated Age range: >= 40 years

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Calverley 2003c *(Continued)*

	Sex: not stated Ethnicity: not stated COPD diagnosis: criteria not stated in abstract, history of smoking Severity of COPD: post-bronchodilator FEV1 = 1.37 to 1.39 L, % predicted FEV1 = 47%, reversibility = 3.54 to 3.72 % predicted FEV1 (from abstract) Inclusion criteria: not stated Exclusion criteria: not stated Baseline characteristics of treatment/control groups: not stated
Interventions	Mometasone furoate once daily 800 µg DPI Placebo 52 weeks
Outcomes	Changes from baseline in post-bronchodilator FEV1 Changes from baseline in COPD symptom scores % of patients with > 1 COPD exacerbation Time to first COPD exacerbation
Notes	Details from Calverley 2003b abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomised" (abstract)
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Information not available

Calverley 2007

Methods	Design: parallel-group Randomisation: yes, method stated Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient department Number eligible: 3096 Number enrolled: 3058 Number in treatment group: 1534 Number in control group: 1524 Number of withdrawals (treatment/control): 587/673 Number completing trial (treatment/control): 947/851

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Calverley 2007 *(Continued)*

	Age range: placebo (mean) 65 years (8.2); ICS (mean) 65 years (8.4) Sex: placebo 1163 M, 361 F; ICS 1157 M, 377 F Ethnicity: placebo 82% white; ICS 82% white COPD diagnosis: FEV1 < 60% predicted, < 10% reversibility in predicted FEV1, FEV1/FER ratio < 70% Severity of COPD: not stated Inclusion criteria: male or female aged 40 to 80 years; current or ex-smokers with smoking history of > 10 pack-years; established Hx of COPD Exclusion criteria: current diagnosis of asthma or respiratory disorders other than COPD; chest radiograph indicating diagnosis other than COPD; had a lung-volume reduction surgery and/or lung transplant; requirement of LTOT at start of study > 12 hour/day; receiving long-term oral corticosteroid therapy; serious, uncontrolled disease likely to interfere with study and/or cause death within the 3-year study period Baseline characteristics of treatment/control groups: not stated
Interventions	FP 500 µg, 2 times a day (1000 µg/day) Placebo
Outcomes	All-cause mortality St George Respiratory Questionnaire Exacerbation rate Serious adverse events Fatal SAEs
Notes	TORCH study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised" - computer-generated numbers
Allocation concealment (selection bias)	Low risk	Quote: "Neither the subject nor the investigator will know to which treatment arm a subject has been allocated" - supplementary protocol
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 38% FP, 44% placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Calverley 2008

Methods	Design: parallel-group (3 groups - QD treatment, bd treatment, placebo) Randomisation: yes, computer generated code Blinding: double-blind, dosing regimens (QD or bd) were not blinded Withdrawals: stated
Participants	Setting: multicentre study (95 sites), multiple country (11)

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Calverley 2008 *(Continued)*

	Number enrolled: 911 Number in treatment group: 616 (308 QD, 308 bd) Number in control group: 295 Number of withdrawals (treatment/control): 194 (94 QD, 100 bd)/125 Number completing trial (treatment/control): 422 (214 QD, 208 bd)/170 Age range: ≥ 40, mean 65 Sex: M 622, F 289 Ethnicity: white = 787, non-white = 124 COPD diagnosis: pre-bronchodilator FEV1/FVC ratio ≤ 70%, post-bronchodilator FEV1 30% to 70% predicted, low post-bronchodilator FEV1 reversibility (< 10% of predicted normal) Severity of COPD: FEV1 50% to < 80% predicted = 266 (29%), FEV1 30% to < 50% predicted = 455 (44%), FEV1 < 30% predicted = 194 (21%) Inclusion criteria: diagnosis of COPD based on currently accepted criteria, and were current smokers who failed a mandatory smoking cessation program or self reported ex-smokers who had stopped smoking ≥ 12 months before the study Exclusion criteria: clinical history of asthma or any other clinically significant medical illness other than COPD, COPD exacerbation within 3 months before the baseline visit, ventilator support for respiratory failure within the past year, lobectomy, pneumonectomy, lung volume reduction surgery, lung cancer within the past 5 years, nasal CPAP or oxygen use > 2 hours per day, initiation of pulmonary rehabilitation within the past 3 months, treatment with chronic or prophylactic antibiotics, inability to use the MF-DPI inhaler, and < 80% adherence in recording diary data between screening and baseline Baseline characteristics of treatment/control groups: comparable
Interventions	MF-DPI 800 µg QD PM MF-DPI 400 µg bd Placebo
Outcomes	Pulmonary function - pre- and post-bronchodilator FEV1, pre- and post-bronchodilator FEF 25% to 75%, pre- and post-bronchodilator FVC Exacerbations - number and severity (hospitalisations, use of both oral steroid and antibiotic, or of oral steroids alone, as opposed to use of antibiotics alone) Symptom scores Health status - SGRQ, SF-36 Safety - adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated code"

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Calverley 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blinding but dosing regimens not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts stated with reasons - similar numbers
Selective reporting (reporting bias)	Low risk	All outcomes reported

Culpitt 1999

Methods	Design: cross-over, 2 weeks washout Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: single-centre study, hospital outpatient clinic Number eligible: 25 Number enrolled: 20 Number in treatment group: 20 Number in control group: 20 Number of withdrawals (treatment/control): 7 (cross-over) Number completing trial (treatment/control): 13 (cross-over) Age range: 43 to 73 years Sex: 13 M, 8 F Ethnicity: not stated COPD diagnosis: FEV1/FVC < 0.7, post-bronchodilator FEV1 < 85% predicted, reversibility < 15% predicted FEV1 Severity of COPD: mean FEV1 49.5 % predicted at baseline Inclusion criteria: stable COPD, smoking history >= 20 pack-years Exclusion criteria: use of inhaled or oral steroids, or exacerbation in previous 6 weeks, asthma, variability of symptoms, atopy Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1000 µg/day) Placebo 2 times a day Metered-dose inhaler via a spacer 4 weeks cross-over
Outcomes	PEFR Use of reliever inhaler Dyspnoea score Cough score Sputum production Sputum colour Spirometry Sputum cytokine and enzyme assays
Notes	Run-in period 2 weeks

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Culpitt 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 7 (cross-over)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Derenne 1995

Methods	Design: parallel-group Randomisation: yes, method not stated Blinding: double-blind Withdrawals: not stated
Participants	Setting: multicentre study Number eligible: not stated Number enrolled: 194 (152 eligible for van Grunsven meta-analysis) Number in treatment group: 81 Number in control group: 71 Number of withdrawals (treatment/control): not stated Number completing trial (treatment/control): not stated Age range: not stated Sex: not stated Ethnicity: not stated COPD diagnosis: FEV1 30% to 60% predicted Severity of COPD: not stated Inclusion criteria: age <= 75 years, "chronic bronchitis", FEV1 30% to 60% predicted, FEV1 reversibility < 10% predicted, PaO2 > 55 mmHg, usual treatment without corticosteroid, no exacerbation in the last 3 months Exclusion criteria: other pulmonary diseases, corticosteroids past 15 days, IgE > 200 IU/mL, eosinophils > 500 x 10E3/mL Baseline characteristics of treatment/control groups: not stated
Interventions	BDP 1500 µg/d MDI Placebo 24 months
Outcomes	Level of FEV1 Level of PEFR Duration of corticosteroid course

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Derenne 1995 *(Continued)*

Notes	Abstract only Details from van Grunsven meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Van Grunsven 1999
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Information not available

Ferreira 2001

Methods	Design: cross-over, 2 weeks washout Randomisation: yes, sealed envelopes Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: single-centre study, hospital outpatient clinic Number eligible: not stated Number enrolled: 20 Number in treatment group: 20 (cross-over) Number in control group: 20 (cross-over) Number of withdrawals (treatment/control): 1 (cross-over) Number completing trial (treatment/control): 19 (cross-over) Age range: mean 69 years Sex: not stated Ethnicity: not stated COPD diagnosis: ATS guidelines Severity of COPD: mean post-bronchodilator FEV1 55% predicted Inclusion criteria: >= 20 pack-year smoking history and abstinence for >= 6 months Exclusion criteria: respiratory tract infection in 6 weeks before study, clinical instability (increased need for medication, emergency care or hospitalisation), other significant medical illnesses affecting eNO, systemic steroids in the month preceding, asthma Baseline characteristics of treatment/control groups: cross-over
Interventions	BDP 500 µg, 2 times a day (1000 µg/d) Matching placebo Metered-dose inhaler 2 weeks
Outcomes	Spirometry Exhaled nitric oxide

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Ferreira 2001 *(Continued)*

	Exhaled breath condensate: hydrogen peroxide
Notes	ICS were withdrawn during run-in, if patients were on ICS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation"
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes reported

Ferreira 2003

Methods	Design: cross-over group Randomisation: yes, method not stated Blinding: double-blind, double-dummy Withdrawals: not stated
Participants	Setting: single centre study Number eligible: 40 Number enrolled: 40 Number in treatment group: 20 Number in control group: 20 Number of withdrawals (treatment/control): not stated Number completing trial (treatment/control): not stated Age range: not stated Sex: not stated Ethnicity: not stated COPD diagnosis: not stated Severity of COPD: not stated Inclusion criteria: not stated Exclusion criteria: not stated Baseline characteristics of treatment/control groups: not stated
Interventions	FP 1000 µg, 1 time a day (1000 µg/day) Placebo
Outcomes	Exhaled nitric oxide levels FEV1 CRQ - dyspnoea, fatigue, emotional function, master 6-minute walk test

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Ferreira 2003 *(Continued)*

Notes	Poster ATS 99th Conference 2003

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "random" (abstract)
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "triple blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Information not available

GSK 2005 (FCO30002)

Methods	Design: parallel-group, 2 weeks run-in and 12 weeks treatment Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: multicentre (32), Germany Number eligible: 210 Number enrolled: 207 Number in groups: FP 68, prednisolone-FP 70, placebo 69 Number of withdrawals: FP 12, prednisolone-FP 8, placebo 10 Number completing trial: FP 56, prednisolone-FP 62, placebo 59 Mean age: FP 61, prednisolone-FP 61, placebo 63 Sex (number F:M): FP 26:40, prednisolone-FP 20:49, placebo 19:47 Ethnicity: not reported COPD diagnosis: not stated Inclusion criteria: documented history of COPD, age 40 to 79, FEV1 40% to 80% predicted, FEV1/FVC < 70%, increase of FEV1 < 10% at 30 minutes post salbutamol, symptomatic on ≥ 5 days and symptom score > 5 and/or salbutamol required, able to use Mini-Wright peak-flow-meter and Diskus inhaler correctly

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GSK 2005 (FCO30002) *(Continued)*

	Exclusion criteria: long-term oxygen therapy, use of inhaled or systemic corticosteroids during 8 weeks prior to study entry, acute exacerbation or antibiotic treatment or hospital stay within 4 weeks before study entry, use of beta-blockers within 2 weeks before study entry Baseline characteristics: comparable
Interventions	Run-in period: all participants received salmeterol 50 µg bd as bronchodilator treatment and salbutamol MDI as rescue medication Treatment-period: salmeterol 50 µg bd was continued throughout the study. At visit 2, participants were randomised into one of 3 groups and received (in addition to salmeterol) either Placebo tablets for 2 weeks plus fluticasone 500 µg bd for 12 weeks OR Prednisolone tablets (20 to 40 mg per day, depending on body weight) plus placebo Diskus™ for 2 weeks, then switch to Fluticasone 500 µg bd for the following 10 weeks OR Placebo tablets for 2 weeks plus Placebo Diskus™ for 12 weeks
Outcomes	Primary: Change in FEV1 (L) after 12 weeks of treatment compared with baseline at randomisation Secondary: participants' self assessment of exercise capacity (oxygen cost diagram) Morning serum cortisol concentrations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" - method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals stated; similar
Selective reporting (reporting bias)	Low risk	All outcomes reported

GSK 2005 (FLTA3025)

Methods	Design: parallel-group, 2 weeks placebo run in then 6 months treatment Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: 55 centres in the United States Number eligible: unknown Number enrolled: 640

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GSK 2005 (FLTA3025) *(Continued)*

	Number in groups: placebo 206, FP 200 216, FP 500 218 Number of withdrawals: placebo 79, FP 250 76, FP 500 71 Number completing trial: placebo 127, FP 250 140, FP 500 147 Mean age: placebo 64.8, FP 250 65.2, FP 500 63.3 Sex (number MF:M): placebo 66:140, FP 250 60:156, FP 500 74:144 Ethnicity (white, n): placebo 196, FP 250 204, FP 500 206 COPD diagnosis: not stated Inclusion criteria: COPD diagnosis; at least 40 years old; current or prior 20 pack-years smoking; productive cough most days for at least 3 months of year, for at least 2 years, and not attributable to another disease process; baseline FEV1 < 65% predicted normal but > 0.70 litres (L) or FEV1 ≤ 0.70 L and > 40% of predicted normal and FEV1/forced vital capacity (FVC) ratio of < 0.70; score of ≥ 2 on the Modified Medical Research Council (MMRC) Dyspnea Scale at screening and a score of ≥ 4 on the CBSQ at randomisation, and had not received systemic corticosteroids or high-dose inhaled corticosteroid therapy for at least 6 months prior to screening Exclusion criteria: current diagnosis of asthma, concurrent participation in a pulmonary rehabilitation programme, a respiratory disease other than COPD or other significant concurrent disease, an abnormal and clinically significant ECG at screening, and the occurrence of a moderate or severe COPD exacerbation during the run-in period. Concurrent use of the following respiratory medications was not allowed: beta-agonists (other than salbutamol), cromolyns, corticosteroids (oral, inhaled and intranasal), anti-leukotrienes and ipratropium. Use of systemic corticosteroids for the treatment of a COPD exacerbation required subject withdrawal. Baseline characteristics: comparable
Interventions	Following the 2-week placebo run-in period, eligible participants were randomised (1:1:1) to 1 of 3 treatments administered via the DISKUS™ multidose powder inhaler for 6 months (24 weeks): FP 250µg bd, FP 500µg bd or placebo bd. Salbutamol was provided as supplemental medication for the duration of the study.
Outcomes	Primary: morning pre-dose FEV1 at endpoint. Endpoint was defined as the last pre-dose FEV1 during the treatment period for each participant. Secondary: Chronic Bronchitis Symptoms Questionnaire (CBSQ) score; Transition Dyspnea Index (TDI) score; exacerbations of COPD (incidence, severity and time to first exacerbation); participant-recorded daily morning peak expiratory flow rate (PEFR); supplemental salbutamol use; and night-time awakenings requiring salbutamol. Quality of life was assessed by the Chronic Respiratory Disease Questionnaire (CRDQ). A mild exacerbation was defined as use of more than 12 puffs or 4 nebules of salbutamol on 2 consecutive days. A moderate exacerbation was defined as use of either antibiotics and/or oral or inhaled corticosteroids for treatment of worsening COPD symptoms, and a severe exacerbation was an exacerbation requiring in-patient hospitalisation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "double blind" - method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated

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GSK 2005 (FLTA3025) *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts stated and reasons given - similar numbers
Selective reporting (reporting bias)	Low risk	All outcomes reported

Guenette 2011

Methods	Design: cross-over group Randomisation: yes, method not stated Blinding: double-blind, placebo-controlled Withdrawals: stated
Participants	Setting: hospital outpatient clinic Number eligible: not stated Number enrolled: 17 Number in groups: 17 (cross-over) Number of withdrawals: 0 Number completing trial: 17 Age range: > 40 years old Sex: 12 M, 5 F Ethnicity: not stated (multicentre) COPD diagnosis: clinically stable COPD patients Severity of COPD: mean FEV1 54% predicted Inclusion criteria: ≥ 40 years with a clinical diagnosis of COPD for at least 1 year, smoking ≥ 20 pack-years, FEV1 ≤ 70% predicted, FEV1/FVC < 0.7, FRC ≥ 120% predicted and moderate to severe chronic activity-related dyspnoea as evidenced by a modified baseline Dyspnoea Index focal score ≤ 6 Exclusion criteria: asthma, other condition leading to dyspnoea, hospitalised or lower respiratory tract infection 4 week prior, oxygen saturation ≤ 80% during exercise Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg twice daily Placebo twice daily 2 weeks (with 2 weeks washout)
Outcomes	Borg dyspnoea score during exercise, cycle endurance, spirometry, lung volumes
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available

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Guenette 2011 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Hanania 2003

Methods	Design: parallel-group Randomisation: yes, method not stated (stratified by reversibility and site) Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient clinic Number eligible: 1489 Number enrolled: 723 Number in groups: FP/SM 178, FP 183, SM 177, placebo 185 Number of withdrawals: FP/SM 53, FP 49, SM 57, placebo 59 Number completing trial: FP/SM 125, FP 134, SM 120, placebo 126 Age range: 40 to 84 years for FP versus placebo Sex: 247 M, 121 F Ethnicity: not stated (multicentre) COPD diagnosis: ATS criteria, FEV1/FVC ratio <= 70%, FEV1 < 65% predicted and > 0.70 L Severity of COPD: mean FEV1 42% predicted Inclusion criteria: current or former smokers with >= 20 pack-year history, chronic bronchitis, moderate dyspnoea Exclusion criteria: current asthma, oral steroids in previous 6 weeks, abnormal clinically significant ECG, long-term oxygen therapy, moderate or severe exacerbation in run-in, significant medical disorder Baseline characteristics of treatment/control groups: comparable
Interventions	FP 250 µg, 2 times a day (500 µg/d) Salmeterol 50 µg, 2 times a day FP 250 µg/salmeterol 50 µg, 2 times a day Placebo Diskus 24 weeks
Outcomes	Predose FEV1 2 hour post dose FEV1 Morning PEFR Dyspnoea (Transitional Dyspnoea Index) Supplemental salbutamol use Health status (CRDQ) Symptoms of chronic bronchitis (CBSQ) Exacerbations Adverse events
Notes	

Risk of bias

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Hanania 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 27% FP, 32% placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Hattotuwa 2002

Methods	Design: parallel-group Randomisation: yes, random number table Blinding: double-blind Withdrawals: stated
Participants	Setting: hospital outpatient clinic Number eligible: not stated Number enrolled: 37 Number in treatment group: 17 Number in control group: 19 Number of withdrawals (treatment/control): 1/5 + 1 insufficient biopsy Number completing trial (treatment/control): 16/14 Age range: 40 to 75 years Sex: 26 M, 4 F Ethnicity: not stated COPD diagnosis: FEV1 25% to 80% of predicted Severity of COPD: mean FEV1 % predicted FP 46.2%, placebo 45.5% Inclusion criteria: current or ex-smokers > 20 pack-years Exclusion criteria: atopy, acute bronchodilator reversibility, severe concurrent medical problems, chest infection within 8 weeks before study Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1,000 µg/d) Placebo Multidose dry powder inhaler (Accuhaler) 3 months
Outcomes	Peak flow Symptom score Spirometry Exhaled carbon monoxide Bronchoscopy Exacerbations
Notes	Run-in 8 weeks

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Hattotuwa 2002 *(Continued)*

	Had steroid trial (prednisolone 30 mg, 2 weeks) after cessation of FP for 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random number table"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals: 1 FP, 5 placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

John 2005

Methods	Design: cross-over group Randomisation: yes, method not stated Blinding: double-blind Withdrawals: not stated
Participants	Setting: not stated Number eligible: not stated Number enrolled: 22 Number in treatment group: 11 Number in control group: 11 Number of withdrawals (treatment/control): not stated Number completing trial (treatment/control): 11/11 Age range: placebo: mean 51.36 years; ICS: mean 61.82 years Sex: 10 M, 12 F Ethnicity: not stated COPD diagnosis: GOLD guidelines (5 patients mild, 6 patients moderate) Severity of COPD: placebo FEV1 99.9% predicted; ICS FEV 77% predicted Inclusion criteria: COPD, clinically stable, no previous hospital admission or treatment change in the last 3 months, none received oral corticosteroids in the preceding 8 weeks Exclusion criteria: current or past Dx of asthma, RTI in past 2 weeks, cancer, thyroid disease, severe liver disease, chronic heart failure Baseline characteristics of treatment/control groups: comparable
Interventions	BDP 400 µg, 2 times a day (800 µg/day) Placebo Short acting β2 agonists or theophylline for symptom relief
Outcomes	SGRQ score - symptom, activity, impact Pulmonary function - FEV1, VC, FVC, PEF, TLC Peripheral blood monocytes IL-10, IFN-γ, MIP-1, GM-CSF

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John 2005 *(Continued)*

	Serum cortisol levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Kerstjens 1992

Methods	Design: parallel-group Randomisation: yes, computer-generated Blinding: double-blind Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient clinic Number eligible: not stated Number enrolled: 274 (whole study); 182 in subgroup of BDP versus placebo Number in treatment group: 91 (BDP) Number in control group: 91 Number of withdrawals (treatment/control): 12/44 Number completing trial (treatment/control): 79/47 Age range: 18 to 60 years Sex: 117 M, 65 F Ethnicity: Caucasian COPD diagnosis: patients with obstructive airways disease and bronchial hyper-responsiveness to histamine (asthma, COPD, asthmatic bronchitis or undefined) were recruited. COPD was diagnosed in current or former smokers without a history of asthmatic attacks who reported either chronic cough with or without sputum production or dyspnoea when walking quietly on level ground, or both Severity of COPD: pre-bronchodilator FEV1 64.6% predicted (BDP group), 63.3% predicted Inclusion criteria: FEV1 between 4.5 and 1.64 residual standard deviations (SDs) below predicted, or the ratio of FEV1 to inspiratory VC was less than 1.64 residual SDs below predicted provided that the TLC was more than 1.64 residual SDs below predicted; bronchial hyper-responsiveness: PC20 (histamine) <= 9 mg/mL Exclusion criteria: presence of major illnesses Baseline characteristics of treatment/control groups: comparable, except that the BDP group was slightly less hyper-responsive
Interventions	Terbutaline 250 µg, 2 puffs, 4 times a day with either: BDP 100 µg, 2 puffs, 4 times a day (800 µg/day)

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Kerstjens 1992 *(Continued)*

	or ipratropium 20 µg, 2 puffs, 4 times a day or placebo Placebo, 2 puffs, 4 times a day Metered-dose inhaler 3 years
Outcomes	FEV1 Bronchodilator reversibility PC20 to histamine
Notes	Run-in period of 4 weeks Study was terminated early because of predefined, significant differences in the withdrawal rate, FEV1 and PC20 Only the ICS versus placebo comparison is analysed in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed by telephoning an independent center that used a computerized minimization method with stratification"
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was performed by telephoning an independent center that used a computerized minimization method with stratification"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind regimens"
Incomplete outcome data (attrition bias) All outcomes	High risk	Rate of withdrawals in corticosteroid group (12 patients) differed from the placebo group (44 patients)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Lapperre 2009

Methods	Design: parallel-group Randomisation: yes, performed by independent randomisation centre Blinding: double-blind Withdrawals: stated, reasons not stated
Participants	Setting: primary care, Netherlands Number eligible: 4617 Number enrolled: 114 Number in treatment group: 26 (FP 30 months), 31 (FP 6 months, then placebo), 28 (FP/salmeterol) Number in control group: 29 Number of withdrawals: 4 (FP 30 months), 3 (FP 6 months, then placebo), 4 (FP/salmeterol), 4 (placebo)

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Lapperre 2009 *(Continued)*

	Number completing trial: 22 (FP 30 months), 23 (FP 6 months, then placebo), 21 (FP/salmeterol), 20 (placebo) Age range: 45 to 75 Sex (M/F): 20/4 (FP 30 months), 22/4 (FP 6 months, then placebo), 23/3 (FP/salmeterol), 22/3 (placebo) Ethnicity: not stated COPD diagnosis: Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II and III Severity of COPD: as above Inclusion criteria: age 45 to 75, current or former smokers, smoked for 10 or more pack-years, lung function levels compatible with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II and III Exclusion criteria: asthma and receipt of ICS within 6 months before random assignment Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500µg twice daily for the first 6 months followed by placebo twice daily for 24 months; FP 500 µg twice daily for 30 months; FP 500 µg twice daily and salmeterol 50 µg twice daily in a single inhaler for 30 months; or placebo twice daily for 30 months
Outcomes	Primary: inflammatory cell counts in bronchial biopsies and induced sputum Secondary: post-bronchodilator spirometry and hyper-responsiveness to methacholine PC20, dyspnoea (modified Medical Research Council dyspnoea scale), health status (St George's Respiratory Questionnaire, Clinical COPD Questionnaire)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised by independent randomisation center"
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts stated - similar
Selective reporting (reporting bias)	Low risk	All outcomes reported

Laptseva 2002

Methods	Design: parallel-group Randomisation: yes, method not stated Blinding: double-blind Withdrawals: not stated
Participants	Setting: not stated Number eligible: 49 Number enrolled: 49 Number in treatment group: 25

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Laptseva 2002 *(Continued)*

	Number in control group: 24 Number of withdrawals (treatment/control): ? Number completing trial (treatment/control): 25/24 Age range: 45 to 65 years Sex: not stated Ethnicity: not stated COPD diagnosis: FEV1 40% to 60% of predicted normal, FEV1/VC < 55%, bronchodilator reversibility of < 15% Severity of COPD: not stated Inclusion criteria: COPD as defined above Exclusion criteria: not stated Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 400 µg, 2 times a day (800 µg/d) Placebo
Outcomes	Number and severity of exacerbations FEV1 FVC FEV50 Diary card symptoms PEFR
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available (Abstract)
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Information not available

LHS 2000

Methods	Design: parallel-group Randomisation: yes, computer generated - correspondence from Melissa Skeans 11 July 2002 - (participants and staff unaware of treatment allocation), stratified by centre and smoking status Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: multicentre study, USA and Canada, hospital outpatient clinics Number eligible: 1347 Number enrolled: 1116

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LHS 2000 *(Continued)*

	Number in treatment group: 559 Number in control group: 557 Number of withdrawals (treatment/control): 28/38 Number completing trial (treatment/control): 531/519 Age range: 40 to 69 years Sex: 704 M, 412 F Ethnicity: non-white race 6.3% of intervention group, 4.1% of placebo group COPD diagnosis: FEV1/FVC < 0.7, FEV1 30% to 90% predicted Severity of COPD: mean post-bronchodilator FEV1 68.5% predicted in intervention group, 67.2% predicted in placebo group Inclusion criteria: current smokers or quit smoking within previous 2 years Exclusion criteria: medical conditions such as cancer, recent myocardial infarction, alcoholism, heart failure, IDDM, neuropsychiatric disorders; use of bronchodilators, oral or inhaled steroids in previous year Baseline characteristics of treatment/control groups: comparable
Interventions	TAA 600 µg, 2 times a day (1200 µg/day) Placebo 2 times a day Metered-dose inhaler (identical) Mean duration 40 months
Outcomes	Change in pre-bronchodilator FEV1 over time Change in pre-bronchodilator FVC over time Change in post-bronchodilator FEV1 over time Change in post-bronchodilator FVC over time Daily cough and phlegm >= 3 months/year Highest dyspnoea level Highest wheezing level No. of new or increased respiratory symptoms categorised as moderate or severe No. of hospitalisations No. of emergency department visits, not resulting in hospitalisation No. of outpatient physician visits No. of health care visits Cause-specific morbidity and mortality PC20 methacholine Health-related quality of life (SF-36) Side effects Bone mineral density
Notes	Intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation....randomly assigned...according to center"
Allocation concealment (selection bias)	Low risk	Quote: "Participants and clinical center staff were unaware of study-drug assignments"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias)	Low risk	Withdrawals: 28 TAA, 38 placebo

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LHS 2000 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All outcomes reported

Llewellyn-Jones 1996

Methods	Design: parallel-group Randomisation: yes, computer-generated (information from GSK, 13 May 2002) Blinding: double-blind, double dummy (information from GSK, 13 May 2002) Withdrawals: stated
Participants	Setting: single-centre study, UK hospital clinic, home diary Number eligible: not stated Number enrolled: 17 Number in treatment group: 8 Number in control group: 9 Number of withdrawals (treatment/control): 0/1 (infective exacerbation) Number completing trial (treatment/control): 8/8 Age range: 50 to 75 years Sex: 8 M, 8 F Ethnicity: not stated COPD diagnosis: smoking-related chronic bronchitis and emphysema Severity of COPD: mean RV/TLC 58.3% predicted, mean KCO 43.4% predicted in placebo group; mean RV/TLC 51.2% predicted, mean KCO 52.7% predicted in treatment group Inclusion criteria: chronic bronchitis and clinical evidence of emphysema (radiological hyperinflation, airflow obstruction, hyperinflation, reduced gas transfer) Exclusion criteria: inhaled or oral steroids in preceding 3 months Baseline characteristics of treatment/control groups: comparable
Interventions	FP 750 µg, 2 times a day (1500 µg/day) Placebo 2 times a day Inhaler, volumatic spacing device 8 weeks
Outcomes	Daily symptoms of breathlessness, cough, general well-being Morning peak flow rate at study completion Evening peak flow rate at study completion Sputum volume and colour (reported) Sputum volume (4-hour collection) Sputum chemotactic activity, elastase inhibitory capacity, albumin concentration, myeloperoxidase activity, fluticasone propionate concentration Blood neutrophil function Serum albumin concentration Acute infective exacerbations Spirometry
Notes	No difference in spirometry reported between intervention and control groups at study completion

Risk of bias

Bias	Authors' judgement	Support for judgement

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Llewellyn-Jones 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 withdrawal from placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported

Loppow 2001

Methods	Design: cross-over, 4 weeks washout Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: single-centre study, Germany, hospital outpatient clinic Number eligible: not stated Number enrolled: 19 Number in treatment group: 19 (cross-over) Number in control group: 19 (cross-over) Number of withdrawals (treatment/control): 0/0 Number completing trial (treatment/control): 19/19 Age range: 31 to 77 years Sex: 12 M, 7 F Ethnicity: not stated COPD diagnosis: chronic bronchitis (ATS criteria, cough and sputum production), current or ex-smokers > 20 pack-years Severity of COPD: mean FEV1 83.4% predicted (2 patients had no airflow obstruction) Inclusion criteria: as for COPD diagnosis; 14 patients had bronchial hyper-responsiveness (PC20 methacholine < 8 mg/mL) Exclusion criteria: use of inhaled or systemic corticosteroids in previous 3 months, respiratory tract infection in previous 4 weeks Baseline characteristics of treatment/control groups: cross-over study
Interventions	FP 1000 µg/day Placebo Delivery device not stated 4 weeks each treatment period (cross-over)
Outcomes	FEV1 VC Exhaled NO Induced sputum cell count Induced sputum fluid-phase markers (LCH, ECP, elastase, IL-8, iNOS)

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Loppow 2001 *(Continued)*

Notes	Chronic bronchitis patients included, not only COPD with airflow obstruction 14/19 patients had bronchial hyper-responsiveness (PC20 MCh < 8 mg/mL) and 6/19 had positive skin prick test

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Mahler 2002

Methods	Design: parallel-group Randomisation: yes, method not stated (stratified by centre and reversibility) Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient clinic Number eligible: 1352 Number enrolled: 691 (645 with evaluable data) Number in groups: SM/FP 165, SM 160, FP 168, placebo 181 Number of withdrawals: SM/FP 52, SM 46, FP 69, placebo 69 Number completing trial: SM/FP 113, SM 114, FP 99, placebo 112 Age range: 42 to 90 years for FP versus placebo Sex: 239 M, 110 F Ethnicity: not stated (multicentre) COPD diagnosis: ATS criteria, FEV1/FVC <= 70%, FEV1 < 65% predicted and more than 0.70 L Severity of COPD: mean 41% predicted Inclusion criteria: current or former smokers with >= 20 pack-year history, chronic bronchitis, dyspnoea Exclusion criteria: current asthma, oral steroid use in previous 6 weeks, abnormal clinically significant ECG, long-term oxygen therapy, moderate or severe exacerbation during run-in, clinically significant medical disorder Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1000 µg/day) Salmeterol 50 µg, 2 times a day FP 500 µg/salmeterol 50 µg, 2 times a day Placebo Diskus

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Mahler 2002 *(Continued)*

	24 weeks
Outcomes	Change in predose FEV1 Change in 2 hour post dose FEV1 Morning PEFR Supplemental salbutamol use Dyspnoea (Transition Dyspnoea Index) Chronic Bronchitis Symptom Questionnaire Exacerbations Chronic Respiratory Disease Questionnaire Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 40% FP, 38% placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Mirici 2001

Methods	Design: parallel-group Randomisation: yes, computer-generated Blinding: double-blind Withdrawals: stated
Participants	Setting: single-centre study, hospital outpatient clinic Number eligible: 96 Number enrolled: 50 Number in treatment group: 25 Number in control group: 25 Number of withdrawals (treatment/control): 5/5 Number completing trial (treatment/control): 20/20 Age range: mean 52 year BUD, mean 54 year placebo Sex: 30 M, 10 F Ethnicity: not stated COPD diagnosis: FEV1 < 70% predicted with no self reported asthma Severity of COPD: mean 64.1% predicted BUD, mean 59.9% predicted placebo Inclusion criteria: FEV1 reversibility with bronchodilator < 15%, smokers

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Mirici 2001 *(Continued)*

	Exclusion criteria: long-term treatment with oral or inhaled corticosteroids within 6 months of study entry, respiratory tract infection in previous 3 months, pregnancy or lactation, other serious systemic diseases Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 400 µg, 2 times a day (800 µg/day) Placebo Turbuhaler 12 weeks
Outcomes	Sputum cell count Spirometry
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation masked, computer generated"
Allocation concealment (selection bias)	Low risk	Quote: "randomisation masked, computer generated"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 withdrawals in both groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Nishimura 1999

Methods	Design: cross-over, no washout Randomisation: yes, computer-generated (correspondence from Dr Koyama, 3 June 2002) Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: single-centre study, Japan, hospital outpatient clinic Number eligible: not stated Number enrolled: 34 Number in treatment group: 34 (cross-over) Number in control group: 34 (cross-over) Number of withdrawals (treatment/control): 4 withdrawals Number completing trial (treatment/control): 30 (cross-over) Age range: > 55 years Sex: 29 M, 1 F (of the 30 who completed the study) Ethnicity: not stated COPD diagnosis: smoking > 20 pack-years, chest radiographs showing hyperinflation, post-bronchodilator FEV1/FVC < 0.7, FEV1 < 80% predicted Severity of COPD: mean FEV1 37.4% predicted Inclusion criteria: stable (no acute exacerbation of airflow obstruction within last 3 months)

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Nishimura 1999 *(Continued)*

	Exclusion criteria: asthma, heart disease, any other significant medical condition, use of inhaled or oral steroids in last 3 weeks Baseline characteristics of treatment/control groups: cross-over
Interventions	BDP 750 µg, 4 times a day (3000 µg/day) Placebo 4 times a day Metered-dose inhaler with spacer device 4 weeks each treatment period (cross-over)
Outcomes	Change from baseline pre-bronchodilator FEV1 Change from baseline pre-bronchodilator FVC Change from baseline post-bronchodilator FEV1 Change from baseline post-bronchodilator FVC Peak flow (last 14 days of 4-week period) Symptoms (last 14 days of 4-week period) Adverse effects Serum osteocalcin Serum cortisol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 4 (cross-over)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Ozol 2005

Methods	Design: parallel-group Randomisation: yes, computer-generated Blinding: double-blind Withdrawals: stated
Participants	Setting: single-centre study, Turkey Number eligible: not stated Number enrolled: 26 Number in treatment group: 13

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Ozol 2005 *(Continued)*

	Number in control group: 13 Number of withdrawals (treatment/control): 1/3 Number completing trial (treatment/control): 12/10 Age range: mean 65 years Sex: 18 M, 4 F Ethnicity: not stated COPD diagnosis: stable mild to moderate COPD (GOLD criteria) (mild = > 80% predicted FEV1; moderate = 50% to 80% predicted FEV1) Severity of COPD: FEV1 61.1% predicted (BUD); FEV1 57.3% predicted (placebo) Inclusion criteria: FEV1/FVC < 70%, FEV1 > 50% predicted; reversibility of < 200 mL with inhaled salbutamol or less than 12% predicted FEV1; stable COPD; no other systemic or pulmonary disease; no therapy with inhaled or systemic corticosteroids within 3 months; no history asthma or atopy Exclusion criteria: not stated Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 400 µg, 2 times a day (800 µg/day) Placebo
Outcomes	Spirometry BAL cell counts and via bronchoscopy IL8 count Weekly diary - change in cough, dyspnoea, sputum production noted
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised by computer-generated, blinded randomisation list"
Allocation concealment (selection bias)	Low risk	Quote: "treatment randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 1 BUD, 2 placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Paggiaro 1998

Methods	Design: parallel-group Randomisation: yes, computer-generated, sealed envelopes Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient clinics: Europe, New Zealand, South Africa Number eligible: 365 entered run-in (of which 84 withdrew before randomisation) Number enrolled: 281 Number in treatment group: 142

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Paggiaro 1998 *(Continued)*

	Number in control group: 139 Number of withdrawals (treatment/control): 19/27 Number completing trial (treatment/control): 123/112 Age range: 50 to 75 years Sex: M, F Ethnicity: not stated COPD diagnosis: European Respiratory Society definition: decreased maximum expiratory flow and slow forced emptying of lung, slowly progressive, irreversible, not changing markedly over several months Severity of COPD: mean pre-bronchodilator FEV1 59% predicted in intervention group, 55% predicted in placebo group Inclusion criteria: current or ex-smokers (>= 10 pack-years), chronic bronchitis, at least one exacerbation each year for previous 3 years, high expectation of experiencing exacerbation during study period, regular productive cough, FEV1 35% to 90% predicted, FEV1/FVC <= 70%, FEV1 reversibility < 15% after 400 µg (MDI) or 800 µg (Diskhaler) salbutamol (or > 15% but < 200 mL) At end of 2-week run-in: required total symptom score of 4 or more from at least 4 of 14 days of run-in to be included Exclusion criteria: abnormal chest radiograph; current use of fluticasone; within last 4 weeks: use of oral or depot steroids, inhaled steroids of > 500 µg/day, antibiotics or hospital admission Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1000 µg/day) Placebo 2 times a day Metered-dose inhaler (identical), spacers in some patients 6 months
Outcomes	Exacerbations (defined as worsening of COPD symptoms, requiring changes to normal treatment: mild, self managed; moderate, treatment by family physician or as hospital outpatient; severe, admission to hospital) Change in FEV1 compared to baseline Change in FVC compared to baseline Treatment efficacy 6-minute walk distance Borg score before and after 6-minute walk Control of symptoms (4-point scale) Morning peak flow rate Evening peak flow rate Symptom scores for cough, breathlessness, sputum volume, sputum colour Use of rescue medications Serum cortisol
Notes	Intention-to-treat analysis Total number of exacerbations in intervention and control groups described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random numbers were computer generated"
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes"
Blinding (performance bias and detection bias)	Low risk	Quote: "double blind"

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Paggiaro 1998 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 19 in fluticasone group, 27 in placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported

Pauwels 1999

Methods	Design: parallel-group Randomisation: yes, method not stated Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: multicentre study, Europe, hospital outpatient clinics Number eligible: 2157 Number enrolled: 1277 Number in treatment group: 634 Number in control group: 643 Number of withdrawals (treatment/control): 176/189 Number completing trial (treatment/control): 458/454 Age range: 30 to 65 years Sex: 923 M, 354 F Ethnicity: not stated COPD diagnosis: post-bronchodilator FEV1 50% to 100% predicted, pre-bronchodilator FEV1/VC ratio < 70%, increase in FEV1 < 10% predicted after 1 mg terbutaline (dry-powder inhaler) Severity of COPD: mean pre-bronchodilator FEV1 76.8% predicted in intervention group, 76.9% predicted in placebo group Inclusion criteria: currently smoking at least 5 cigarettes/day, smoked for at least 10 years or smoking history at least 5 pack-years, change in FEV1 between end of 1st and end of 2nd 3 month run-in phases < 15%, > 75% compliance with inhaler Exclusion criteria: history of asthma, allergic rhinitis, allergic eczema; use of oral steroids > 4 weeks during preceding 6 months Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 400 µg, 2 times a day (800 µg/day) Placebo 2 times a day Dry powder inhaler (Turbuhaler) 3 years
Outcomes	Change in post-bronchodilator FEV1 over time Adverse events Skin bruises > 50 mm diameter Vertebral fractures on radiographs Bone mineral density
Notes	Run-in phase: 3-month smoking cessation programme Continuing smokers had further 3 months of inhaled medication to check compliance Intention-to-treat analysis Data reported as non-normal

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Pauwels 1999 *(Continued)*

Results:
0 to 6 month: FEV1 improved by median 17 mL/year in intervention group, declined by median 81 mL/year in placebo group (P < 0.001)
9 to 36 month: FEV1 declined by median 57 mL/year in intervention group, declined by median 69 mL/year in placebo group (P = 0.39)

Stratification by smoking history:
<= 36 pack-years: FEV1 declined by median 120 mL in 3 year in intervention group, declined by median 190 mL in 3 year in placebo group (P < 0.001)
> 36 pack-years: FEV1 declined by median 150 mL in 3 year in intervention group, declined by median 160 mL in 3 year in placebo group (P = 0.57)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 176 BUD, 189 placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Renkema 1996

Methods	Design: parallel-group Randomisation: yes, computer-generated, stratified for smoking Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: single-centre study, The Netherlands, hospital outpatient clinic Number eligible: not stated Number enrolled: 39 (of the 58 in the 3 arms of the study) Number in treatment group: 21 Number in control group: 18 Number of withdrawals (treatment/control): 2/5 Number completing trial (treatment/control): 19/13 Age range: adult, < 70 years Sex: 58 M, 0 F Ethnicity: not stated COPD diagnosis: clinical diagnosis of COPD based on history (persistent dyspnoea, mainly on exertion, without sudden attacks of dyspnoea), FEV1 < 80% predicted, RV > 100% predicted, Severity of COPD: mean FEV1 67% predicted in intervention group, 60% predicted in placebo group Inclusion criteria: smokers or ex-smokers, stable phase of disease, specific compliance post-bronchodilator > 100% predicted (or < 100% allowed if air trapping > 1.5 L)

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Renkema 1996 *(Continued)*

	Exclusion criteria: allergy (positive skin prick test, total serum IgE > 200 IU/mL, blood eosinophils > 250 x 10^3/mL), older than 70 years, receiving continuous steroid therapy, severe concomitant disease, abnormal alpha1-antitrypsin serum levels Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 800 µg, 2 times a day (1600 µg/day) Placebo 2 times a day Metered-dose inhaler and spacer (Nebuhaler) 2 years
Outcomes	Change in pre-bronchodilator FEV1 over time Cough score Sputum score Wheeze score Dyspnoea score Complaint score Exacerbations Plasma cortisol
Notes	Run-in period: 3 months Third treatment arm: BUD 800 µg, 2 times a day (1600 µg/d) plus oral prednisolone 5 mg once daily (data not included for this review) Steroid responsiveness assessed by oral prednisolone 40 mg/day for 8 days Medians presented for decline in FEV1, due to skewness and large spread of distribution

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "allocated blindly (by computerized randomisation stratified for smoking)"
Allocation concealment (selection bias)	Low risk	Quote: "allocated blindly (by computerized randomisation stratified for smoking)"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals from BUD group, 5 withdrawals from placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported

Robertson 1986

Methods	Design: cross-over, 2 weeks washout Randomisation: yes, method not stated (correspondence from Professor Burge - 15 October 2002: double-blind, allocation concealment used) Blinding: double-blind, double-dummy

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Robertson 1986 *(Continued)*

	Withdrawals: stated
Participants	Setting: single-centre study, hospital outpatient clinic Number eligible: 83 Number enrolled: 83 Number in treatment group: 83 (cross-over) Number in control group: 83 (cross-over) Number of withdrawals (treatment/control): not stated Number completing trial (treatment/control): not stated Age range: mean 61 years (SD 10) Sex: 66 M, 17 F Ethnicity: no stated COPD diagnosis: FEV1 < 70% predicted Severity of COPD: mean FEV1 44% predicted Inclusion criteria: COPD of at least 5 years duration, chronic bronchitis on MRC questionnaire, 92% were current or ex-smokers Exclusion criteria: asthma, steroid therapy in previous 6 months Baseline characteristics of treatment/control groups: comparable (cross-over)
Interventions	BDP 500 µg, 3 times a day (1500 µg/day) Placebo 3 times a day Metered-dose inhaler 2 weeks each treatment period (cross-over)
Outcomes	FEV1 in treatment period compared to baseline or placebo FVC in treatment period compared to baseline or placebo PEFR in treatment period compared to baseline or placebo
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Correspondence from Professor Burge - double-blind, allocation concealment used Comment: probably done
Allocation concealment (selection bias)	Low risk	Correspondence from Professor Burge - double-blind, allocation concealment used
Blinding (performance bias and detection bias) All outcomes	Low risk	Correspondence from Professor Burge - double-blind, allocation concealment used
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	Outcomes all reported

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Rutgers 1998

Methods	Design: parallel-group Randomisation: yes, computer-generated (correspondence from Dr Rutgers, 2 June 2002) Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: single-centre study, The Netherlands, hospital outpatient clinic Number eligible: 49 Number enrolled: 44 Number in treatment group: 22 Number in control group: 22 Number of withdrawals (treatment/control): 1/4 Number completing trial (treatment/control): 21/18 Age range: 45 to 75 years Sex: 35 M, 9 F Ethnicity: not stated COPD diagnosis: American Thoracic Society criteria Severity of COPD: mean FEV1 58% predicted in intervention group, 62% predicted in placebo group Inclusion criteria: current smoker, FEV1 and FEV1/VC < % predicted minus 1.64 residual SD, increase in FEV1 < 10% predicted after 1 mg terbutaline via Turbuhaler, hyper-responsiveness to MCh (PC20 MCh < 8.0 mg/mL) and AMP (PC20 AMP <= 80 mg/mL) Exclusion criteria: history of atopy, positive skin test, for aeroallergens, specific serum IgE for aeroallergens, serum eosinophil count > 400 x 10^9/mL; in 1 month prior to study: acute upper respiratory tract infection, use of oral or inhaled steroids, antibiotics, mucolytics, theophylline Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 1600 µg/day Placebo Dry powder inhaler (Turbuhaler) 6 weeks
Outcomes	Pre-bronchodilator FEV1 MCh challenge AMP challenge Symptom score Bronchodilator use Morning peak flow Evening peak flow Serum IL-8 Serum histamine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated (correspondence from Dr Rutgers, 2/6/2002)
Allocation concealment (selection bias)	Unclear risk	Computer generated (correspondence from Dr Rutgers, 2/6/2002)
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind, double-dummy"

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Rutgers 1998 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 1 BUD, 4 placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Schermer 2009

Methods	Design: parallel-group Randomisation: yes, randomisation list generated by statistician Blinding: double-blind Withdrawals: stated
Participants	Setting: 44 general practices, Netherlands Number eligible: 442 Number enrolled: 300 Number in groups: FP 94, NAC 96, placebo 96 Number of withdrawals: FP 39, NAC 44, placebo 40 Number completing trial: FP 55, NAC 55, placebo 56 Mean age: FP 58.4, NAC 59.2, placebo 59.6 % male: FP 69, NAC 75, placebo 65 Ethnicity: not stated Inclusion criteria: age 35 to 75 years; current or former smoker; chronic dyspnoea, sputum production and cough for at least 3 consecutive months per year during the previous 2 years; post-bronchodilator FEV1 < 90% of the predicted value, and/or post-bronchodilator FEV1/FVC (forced vital capacity) of the predicted value < 88% for men and < 89% for women Exclusion criteria: post-bronchodilator FEV1 < 40% of predicted and/or a history of asthma, allergic rhinitis or allergic eczema Baseline characteristics of treatment/control groups: comparable
Interventions	2 week run-in with oral prednisolone, then 3 years fluticasone propionate 500 mg twice daily administered as dry powder inhalation by Diskus, oral N-acetylcysteine 600 mg once daily in the morning, or matching placebo treatment
Outcomes	Primary: exacerbation rate, quality of life measured with the Chronic Respiratory Questionnaire (CRQ) Secondary: FEV1 decline, respiratory symptoms
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation list generated by statistician
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind"

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Schermer 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts stated - similar numbers
Selective reporting (reporting bias)	Low risk	All outcomes reported

SCO30002 2005

Methods	Design: parallel-group Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient clinic Number eligible: 300 Number enrolled: 256 Number in treatment group: 131 FP arm Number in control group: 125 Number of withdrawals (treatment/control): 34/40 Number completing trial (treatment/control): 97/85 Age range: mean age 64.6 years FP arm, 65.7 placebo arm Sex: 209 M, 47 F Ethnicity: 100% Caucasian COPD diagnosis: pre-bronchodilator baseline FEV1/VC < 88% for men and < 89% for women of predicted normal and FEV1 < 70% of predicted normal, but > 800 mL Inclusion criteria: aged > 40 years, established clinical history of COPD, poor reversibility of airflow obstruction (< 10% increase of FEV1) after bronchodilator, current or ex-smokers with smoking history of at least 10 pack-years Exclusion criteria: not stated Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1000 µg/day) Placebo
Outcomes	No of COPD exacerbations Number of withdrawals due to COPD exacerbations FEV1 pre-bronchodilator FEV1/VC FVC Record card symptoms - cough, breathlessness Use of relief bronchodilator PEFR Shuttle walking test Borg scale St George Respiratory Questionnaire Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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SCO30002 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 26% FP, 32% placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Senderovitz 1999

Methods	Design: parallel-group Randomisation: yes, method not stated, separately randomised groups based on oral prednisolone response (groups: reversible FEV1 response > 15% and < 30%, irreversible FEV1 < 15%) Blinding: double-blind, double-dummy Withdrawals: stated for the reversibility trial and reversible participants, not clearly described for irreversible participants
Participants	Setting: multicentre study, Denmark, hospital outpatient clinics Number eligible: 40 Number enrolled: 37 (35 with no steroid reversibility, 2 with steroid reversibility) Number in treatment group: awaiting information Number in control group: awaiting information Number of withdrawals (treatment/control): awaiting information Number completing trial (treatment/control): 14/12 (no steroid reversibility arm) Age range: 18 to 75 years Sex: 14 M, 12 F (in the steroid-irreversible group randomised) Ethnicity: not stated COPD diagnosis: FEV1/FVC < 0.7, post-bronchodilator FEV1 > 40% and < 70% predicted, increase in FEV1 < 15% after 0.5 mg terbutaline via Turbuhaler Severity of COPD: median FEV1 1.46 L in the intervention group, median 1.63 in the placebo group Inclusion criteria: stable COPD Exclusion criteria: clinical evidence of asthma (e.g. pollen season-related symptoms, exercise-induced symptoms only, significantly elevated levels of blood eosinophils and IgE), history of atopy (hay fever and/or atopic dermatitis); treatment with oral steroids, sodium cromoglycate or nedocromil in last 4 weeks; other systemic disease making compliance and participation difficult; pregnancy and breast feeding; increase in FEV1 < 30% of baseline after 2 week of prednisolone Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 400 µg, 2 times a day (800 µg/day) Placebo 2 times a day Dry powder inhaler (Turbuhaler) 6 months
Outcomes	Spirometry Exacerbations

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Senderovitz 1999 *(Continued)*

	Symptom score Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals in BUD or placebo arms
Selective reporting (reporting bias)	Low risk	All outcomes reported

Shaker 2009

Methods	Design: parallel-group Randomisation: yes, computer-generated sequence Blinding: double-blind Withdrawals: stated
Participants	Setting: single-centre study, Denmark Number eligible: unknown Number enrolled: 278 Number in treatment group: 127 Number in control group: 127 Number of withdrawals (treatment/control): 55/62 Number completing trial (treatment/control): 72/65 Mean age (treatment/control): 63.6/63.6 Sex (% male treatment/control): 62/54 Ethnicity: not stated COPD diagnosis: FEV1 ≤ 70% predicted, FEV1/FVC ≤ 60% and no reversibility to β2-agonists and oral corticosteroids Severity of COPD: FEV1 % of predicted treatment/control: 51/53 Inclusion criteria: aged 50 to 80 years; current smokers; clinical diagnosis of COPD for not less than 2 years; significant smoking history of at least 10 cigarettes per day during the last 6 months and a previous history of at least 20 pack-years; FEV1 35% to 70% of predicted (pre-bronchodilator) and FEV1/forced vital capacity (FEV1/FVC) ≤ 60% Exclusion criteria: ex-smokers; reversibility of ≥ 12% and 200 mL in FEV1 from baseline values, 15 minutes after inhalation of 1 mg terbutaline or ≥ 15% and 300 mL after 2 weeks on oral prednisolone (25 mg); severe concomitant disease; exacerbation within 30 days prior to the first visit; received oral steroids for more than 4 weeks within 6 months of the first visit; long-term oxygen therapy Baseline characteristics of treatment/control groups: comparable

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Shaker 2009 *(Continued)*

Interventions	2-week run-in period on oral prednisolone (25 mg once daily). Patients with reversibility less than 15% or 300 mL from baseline FEV1 values were then randomly assigned to twice-daily treatment with either 400 µg of budesonide (Pulmicort Turbuhaler) or placebo.
Outcomes	Primary: change over time in the 15th percentile density (PD15) on CT scan (a measure of lung density) Secondary: change over time in the relative area of emphysema at a threshold of –910 Hounsfield units (RA-910), FEV1 and dif- fusion capacity (DLCO) and the number of exacerbations, which was defined as a combination of 2 of the 3 following criteria: increased dyspnoea, increased sputum production and change in sputum colour
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated code"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts stated - similar numbers
Selective reporting (reporting bias)	Low risk	All outcomes reported

Sin 2004

Methods	Design: parallel-group, 4-week run-in Randomisation: yes, method not stated Blinding: double-blind, double-dummy Withdrawals: not stated
Participants	Setting: single centre study, Canada Number eligible: 43 Number enrolled: 41 Number in treatment group: 15 Number in control group: 12 Number of withdrawals (treatment/control): 0/0 Number completing trial (treatment/control): 15/12 Age range: 64 yr 9 Sex: 29 M, 12F

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Sin 2004 *(Continued)*

	Ethnicity: Not stated COPD diagnosis: post-bronchodilator FEV1 25-90%; FEV1/FVC <75% Severity of COPD: FP: FEV1 1.83 L; 56% pred; Placebo: 1.79 L; 61% pred Inclusion criteria: Stable COPD symptoms 3 months prior; History of at least 10 pack-years of smoking or prolonged exposure to noxious gases Exclusion criteria: Not stated Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1000 µg/d) Placebo
Outcomes	Serum CRP Cytokine levels - IL6, MCP-1 FEV1 as % baseline
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Sin 2008

Methods	Design: parallel-group with run-in period Randomisation: yes, method not stated Blinding: double-blind Withdrawals: stated
Participants	Setting: multicentre (11 centres) Number eligible: 356 Number enrolled: 289

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Sin 2008 *(Continued)*

	Number in groups: 45 placebo, 87 FP 500 bd, 92 FP/salmeterol 500 bd Number of withdrawals: 77 Number completing trial: 212 Age range: mean 69.3 +/- 9.3yrs Sex: 63% male Ethnicity: not stated COPD diagnosis: GOLD criteria Severity of COPD: FEV1 47.4 +/- 15.9% pred, FVC 74.4 +/- 16.3% pred Inclusion criteria: not specified Exclusion criteria: not specified Baseline characteristics of treatment/control groups: comparable
Interventions	Run-in phase of FP 500mg bd for 4 weeks, followed by a medication withdrawal phase wherein ICS, LABAs, and theophylline products were withdrawn for 4 weeks. All other medications, including short-acting b2-adrenoceptor agonists, anticholinergics, and tiotropium, were permitted during all phases of the study. Participants were then randomly assigned to one of three arms: placebo, inhaled FP 500 mg bd or inhaled FP/salmeterol combination 500/50 mg bd.
Outcomes	Primary endpoint - C-reactive protein (CRP) level. Secondary endpoints - IL-6, surfactant protein D (SP-D), SGRQ, FEV1 % predicted, FVC % predicted
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar withdrawal rates between arms
Selective reporting (reporting bias)	Low risk	All outcomes reported

Szafranski 2003

Methods	Design: parallel group Randomisation: yes, method not stated

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Szafranski 2003 *(Continued)*

	Blinding: double blind, double dummy
	Withdrawals: stated
Participants	Setting: multicentre study, hospital outpatient clinic
	Number eligible: 980
	Number enrolled: 812
	Number in groups: Combined 208, BUD 198, FM 201, placebo 205
	Number of withdrawals: Combined 59, BUD 62, FM 64, control 90
	Number completing trial: Combined 149, BUD 136, FM 137, control 115 (total 537)
	Age range: mean 64 yr
	Sex: 639M, 173F
	Ethnicity: not stated (multicentre)
	COPD diagnosis: GOLD guidelines
	Severity of COPD: mean FEV1 36% predicted
	Inclusion criteria: outpatients aged >=40 yr, COPD symptoms >=2 yr, smoking history >=10 pack-yrs, FEV1/VC <=70%, FEV1 <50% predicted, total symptom score >=2/day during at least 7 days of run-in, use of short-acting inhaled bronchodilators, >=1 severe COPD exacerbation within 2-12 months before study
	Exclusion criteria: asthma, seasonal allergic rhinitis before age 40, relevant cardiovascular disorders, current respiratory tract diseases or disorders, regular oxygen therapy, exacerbation during run-in, patients in whom it was considered unethical to withdraw inhaled steroids
	Baseline characteristics of treatment/control groups:
Interventions	budesonide/formoterol 160/4.5 µg, 2 inhalations, 2 times a day (640 µg/d of BUD)
	BUD 200 µg, 2 inhalations, 2 times a day (800 µg/d)
	formoterol 4.5 µg, 2 times a day
	placebo
	Turbuhaler
	12 months
Outcomes	Exacerbations
	Morning and evening COPD symptoms
	short-acting beta-agonist use
	PEFR
	Spirometry
	SGRQ
	adverse events
Notes	Trial of combined therapy versus monotherapy versus placebo

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Szafranski 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Relatively high withdrawal rates
Selective reporting (reporting bias)	Low risk	All outcomes reported

Tashkin 2008

Methods	Design: parallel group Randomisation: yes, computer generated Blinding: double-blind, double-dummy Withdrawals: stated
Participants	Setting: 194 centres in the US, Czech Republic, the Netherlands, Poland and South Africa Number eligible: 1942 Number enrolled: 1704 Number in groups: BUD/FM 320/9mcg 277, BUD/FM 160/9mcg 281, BUD 320mcg + FM 9mcg 287, BUD 320mcg 275, FM 9mcg 284, placebo 300 Number of withdrawals: BUD/FM 320/9mcg 39, BUD/FM 160/9mcg 38, BUD 320mcg + FM 9mcg 48, BUD 320mcg 63, FM 9mcg 61, placebo 77 Number completing trial: BUD/FM 320/9mcg 238, BUD/FM 160/9mcg 243, BUD 320mcg + FM 9mcg 239, BUD 320mcg 212, FM 9mcg 223, placebo 223 Age range: BUD/FM 320/9mcg 41-86, BUD/FM 160/9mcg 40-90, BUD 320mcg + FM 9mcg 40-84, BUD 320mcg 40-90, FM 9mcg 42-89, placebo 40-86 Sex (% male): BUD/FM 320/9mcg 67.9, BUD/FM 160/9mcg 64.4, BUD 320mcg + FM 9mcg 74.2, BUD 320mcg 67.6, FM 9mcg 65.5, placebo 69.0 Ethnicity (% white): BUD/FM 320/9mcg 94.2, BUD/FM 160/9mcg 93.2, BUD 320mcg + FM 9mcg 92.0, BUD 320mcg 94.2, FM 9mcg 92.3, placebo 94.7 COPD diagnosis: GOLD criteria Severity of COPD: as below

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Tashkin 2008 *(Continued)*

	Inclusion criteria: aged ≥40; symptoms for >2 years; history of at least one COPD exacerbation treated with a course of oral corticosteroids and/or antibacterials within 1–12 months before screening; documented use of an inhaled short acting bronchodilator as rescue medication; moderate to very severe COPD with a pre-bronchodilator FEV1 of ≤50% of predicted normal and a pre-bronchodilator FEV1/forced vital capacity of <70%; smoking history of ≥10 pack-years; score of ≥2 on the Modified Medical Research Council dyspnoea scale at the time of screening; breathlessness, cough and sputum scale (BCSS) score of ≥2 per day for at least half of the 2-week run-in period Exclusion criteria: history of asthma; history of allergic rhinitis before 40 years of age; significant/unstable cardiovascular disorder; clinically significant respiratory tract disorder other than COPD; homozygous α-1 antitrypsin deficiency or any other clinically significant co-morbidities that could preclude participation in the study or interfere with the study results, as determined by the investigator; required additions or alterations to their usual COPD maintenance therapy or an increment in rescue therapy due to worsening symptoms within 30 days before screening or during the run-in period; oral or ophthalmic non-cardioselective β- adrenoceptor antagonists; oral corticosteroids; pregnancy; breast-feeding Baseline characteristics of treatment/control groups: comparable
Interventions	After 2 weeks of treatment based on previous therapy (ICSs and short-acting bronchodilators allowed during the run-in period), patients received one of the following treatments administered twice daily, for 26 weeks: budesonide/formoterol pMDI 160/4.5 µg × two inhalations (320/9 µg); budesonide/formoterol pMDI 80/4.5 µg × two inhalations (160/9 µg); budesonide pMDI 160 µg × two inhalations (320 µg) plus formoterol DPI 4.5 µg × two inhalations (9 µg); budesonide pMDI 160 µg × two inhalations (320 µg); formoterol DPI 4.5 µg × two inhalations (9 µg); or placebo.
Outcomes	Primary: Pre-dose forced expiratory volume in 1 second (FEV1), 1-hour post-dose FEV1 Secondary: morning and evening PEF (L/min)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Computer generated code
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar rates of withdrawal between ICS and placebo arms
Selective reporting (reporting bias)	Low risk	All outcomes reported

Thompson 1992

Methods	Design: parallel group Randomisation: yes, table of random numbers

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Thompson 1992 *(Continued)*

	Blinding: double blind, double dummy
	Withdrawals: stated
Participants	Setting: community
	Number eligible: not stated
	Number enrolled: 31
	Number in treatment group: 31 in total in treatment or control groups
	Number in control group: 31 in total in treatment or control groups
	Number of withdrawals (treatment/control): 1 withdrawal (unspecified as to which group)
	Number completing trial (treatment/control): 20/10
	Age range: mean age 50.6 yr in intervention group, mean age 47.0 yr in placebo group
	Sex: 15M, 15F
	Ethnicity: not stated
	COPD diagnosis: chronic bronchitis (chronic productive cough for most days of each month for at least 2 consecutive years)
	Severity of COPD: mean FEV1 72.6% predicted in intervention group, mean FEV1 72.0% predicted in the placebo group
	Inclusion criteria: current cigarette smoking, airflow obstruction with FEV1/FVC <75%, improvement of FEV1/FVC to not more than 75% with bronchodilator
	Exclusion criteria: seasonal or episodic dyspnoea, wheezing, atopy, other active lung disease, DLCO <50%, infiltrates on chest xray; use of oral or inhaled steroids or inhaled cromolyn within previous 3 months; carbon dioxide retention; cardiac disease or other contraindication to bronchoscopy
	Baseline characteristics of treatment/control groups: higher smoking history in intervention group (with similar exhaled carbon monoxide levels)
Interventions	BDP µg, 4 times a day (µg/d)
	Placebo 4 times a day
	metered-dose inhaler
	6 weeks
Outcomes	FEV1 FVC MMEFR PEFR Sputum production Exhaled carbon monoxide levels Bronchoscopy visual bronchitis index Bronchoalveolar lavage cell count and parameter Rescue bronchodilator usage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Thompson 1992 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "randomised using a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Thompson 2002

Methods	Design: crossover, no washout Randomisation: yes, computer generated Blinding: double blind, double dummy Withdrawals: stated
Participants	Setting: single centre study, hospital outpatient clinic Number eligible: not stated Number enrolled: 52 Number in treatment group: 52 (crossover) Number in control group: 52 (crossover) Number of withdrawals (treatment/control): 4/12 Number completing trial (treatment/control): 36 (crossover) Age range: 48 to 80 yr Sex: 36M Ethnicity: not stated COPD diagnosis: ATS guidelines Severity of COPD: pre-bronchodilator FEV1 1.1L Inclusion criteria: >=30 pack-year smoking, FEV1/FVC <60%, pre-bronchodilator FEV1<80% predicted, daily use of beta-agonists and/or ipratropium Exclusion criteria: inhaled or systemic steroids in 30 days prior; family or personal history of asthma; atopy, allergic rhinitis, nasal polyposis, pulmonary disease other than COPD, heart failure, lung cancer Baseline characteristics of treatment/control groups: crossover
Interventions	FP 220 µg, 2 puffs, 2 times a day (880 µg/d)

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Thompson 2002 *(Continued)*

	identical-appearing placebo inhaler
	metered-dose inhaler
	3 months
Outcomes	lung function tests
	arterial blood gases
	QOL (Chronic Respiratory Questionnaire)
	exacerbation
	respiratory symptoms
	adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated random number table"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 withdrawals from placebo, 4 withdrawals from ICS
Selective reporting (reporting bias)	Low risk	All outcomes reported

van Grunsven 1999

Methods	Meta-analysis of Derenne, Kerstjens and Renkema
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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van Grunsven 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded studies
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Information not available

van Grunsven 2003

Methods	Design: parallel group
	Randomisation: yes, method not stated
	Blinding: Not Specified, Placebo controlled
	Withdrawals: Stated
Participants	Setting: hospital outpatient clinic, single centre, the Netherlands
	Number eligible: 74
	Number enrolled: 48
	Number in treatment group: 24
	Number in control group: 24
	Number of withdrawals (treatment/control): 6/6
	Number completing trial (treatment/control): 18/18
	Age range: mean 46.5yr
	Sex: 25M, 23F
	Ethnicity: Not specified
	COPD diagnosis: EARLY COPD
	Severity of COPD: FEV1 98% pred (FP); FEV1 99% pred (Placebo)
	Inclusion criteria: Chronic cough sputum production at least 3 consecutive months and annual decline in pre-bronchodilator FEV1 40-80mL
	Exclusion criteria: Previous Dx of pulmonary condition; co-morbid condition with reduced life expectancy; intolerance for inhaled 2-agonists; use of 2-blocking agents; inability to use inhalation devices or peak-flow meters
	Baseline characteristics of treatment/control groups:

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van Grunsven 2003 *(Continued)*

	Comparable
Interventions	FP 250 µg, 2 times a day (500 µg/day) Placebo
Outcomes	Annual decline of post-bronchodilator FEV1 Decline of pre-bronchodilator FEV1 PC20 Histamine Exacerbation rate Number of episodes with aggravated symptoms Use of rescue bronchodilators Symptom score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	25% withdrawal rate overall
Selective reporting (reporting bias)	Low risk	All outcomes reported

Verhoeven 2002

Methods	Design: parallel group Randomisation: yes, method not stated Blinding: double blind, double dummy Withdrawals: stated
Participants	Setting: single centre study, hospital outpatient clinic Number eligible: not stated Number enrolled: 23 COPD; also studied 6 asymptomatic smokers Number in treatment group: 10 Number in control group: 13 Number of withdrawals (treatment/control): 0/0

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Verhoeven 2002 *(Continued)*

	Number completing trial (treatment/control): 10/13 Age range: 42 to 67 yr Sex: 19M, 4F Ethnicity: not stated COPD diagnosis: chronic productive cough, FEV1 <=70% predicted Severity of COPD: mean FEV1 66% predicted FP, mean FEV1 61% predicted placebo Inclusion criteria: non-specific BHR (PC20 histamine <=8 mg/ml), current smoker, FEV1 reversibility <10% after terbutaline, normal serological examination (Phadiatop test), negative skin prick tests for aeroallergens Exclusion criteria: asthma, respiratory tract infection in previous 4 weeks, serious or unstable concomitant disease Baseline characteristics of treatment/control groups: comparable
Interventions	FP 500 µg, 2 times a day (1,000 µg/d) placebo Diskhaler 6 months
Outcomes	BHR methacholine Bronchial biopsies Lung function tests Serum cortisol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

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Vestbo 1999

Methods	Design: parallel group Randomisation: yes, computer generated Blinding: double blind, double dummy Withdrawals: stated
Participants	Setting: population cohort (Copenhagen City Heart Study), Denmark Number eligible: 1118 (of which 828 were excluded during screening) Number enrolled: 290 Number in treatment group: 145 Number in control group: 145 Number of withdrawals (treatment/control): 36/51 Number completing trial (treatment/control): 109/94 Age range: 30 to 70 yr Sex: 175M, 115F Ethnicity: all subjects living in Copenhagen COPD diagnosis: FEV1/VC ratio <=0.7 and no self-reported asthma Severity of COPD: mean post-bronchodilator FEV1 86.2% in intervention group, 86.9% in placebo group Inclusion criteria: age 30-70 yr, FEV1/VC ratio <=0.7, FEV1 reversibility <15% baseline with 1 mg terbutaline from Turbuhaler, oral steroid response (15 mg prednisolone 10 days) <15% baseline Exclusion criteria: long term treatment (>2 episodes of >4 wk) with oral or inhaled steroids within previous 6 month, pregnancy or lactation, intention to become pregnant, other serious systemic disease, chronic alcohol or drug use Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 800 µg morning, 400 µg evening for 6 month (1200 µg/d), then BUD 400 µg, 2 times a day for 30 month (800 µg/d) Placebo 2 times a day Dry powder inhaler (Turbuhaler) (identical) 3 years
Outcomes	FEV1 decline rate Symptoms Exacerbations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation sequence generated by computer"

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Vestbo 1999 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was masked"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar rates of withdrawal between arms. Withdrawals: 36 BUD, 51 placebo
Selective reporting (reporting bias)	Low risk	All outcomes reported

Weiner 1995

Methods	Design: crossover, 4 weeks washout Randomisation: yes, method not stated Blinding: double blind, double dummy Withdrawals: stated
Participants	Setting: single centre study, hospital outpatient clinic Number eligible: 30 (of whom 22 were bronchodilator non-responders, defined as >20% increase in FEV1) Number enrolled: 30 (of whom 22 were bronchodilator non-responders) Number in treatment group: 22 bronchodilator non-responders (crossover, included in this review) Number in control group: 2 bronchodilator non-responders (crossover, included in this review) Number of withdrawals (treatment/control): 0 Number completing trial (treatment/control): 30 Age range: 55 to 77 yr Sex: 14M, 8F Ethnicity: not stated COPD diagnosis: chronic airflow limitation Severity of COPD: mean FEV1 1.39L Inclusion criteria: stable condition, smoking history >30 pack-yrs, FEV1<50% predicted, FEV1/FVC<60% Exclusion criteria: asthma, seasonal or episodic dyspnoea or wheezing, family history of asthma, improvement of FEV1/FVC to more than 70%, use of oral or inhaled steroids within previous 3 months Baseline characteristics of treatment/control groups: crossover
Interventions	BUD 400 µg, 2 times a day (800 µg/d) Placebo 2 times a day metered-dose inhaler via spacer 6 weeks each treatment period (crossover)
Outcomes	Change in FEV1 from baseline Rescue bronchodilator usage
Notes	
Risk of bias	

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Weiner 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Method not stated
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Weiner 1999

Methods	Design: crossover, 4 weeks washout
	Randomisation: yes, method not stated
	Blinding: double blind, double dummy
	Withdrawals: stated
Participants	Setting: single centre study, Israel, hospital outpatient clinic
	Number eligible: not stated
	Number enrolled: 168 (124 bronchodilator non-responders, 44 bronchodilator responders)
	Number in treatment group: 124 bronchodilator non-responders (crossover, included in this review)
	Number in control group: 124 bronchodilator non-responders (crossover, included in this review)
	Number of withdrawals (treatment/control): 7 withdrawals
	Number completing trial (treatment/control): 117 (crossover)
	Age range: mean 64.4 yr (bronchodilator non-responders)
	Sex: 102M, 66F
	Ethnicity: not stated
	COPD diagnosis: chronic airflow limitation on spirometry, without evidence of asthma
	Severity of COPD: mean post-bronchodilator FEV1 1.34L
	Inclusion criteria: stable, smoking >30 pack-yr, FEV1 <50% predicted, FEV1/FVC <60%
	Exclusion criteria: physician diagnosis of asthma, seasonal or episodic dyspnoea or wheezing, family history of asthma, atopy (history of allergy and positive skin prick test to common antigens), improvement of FEV1/FVC to >70% with inhaled beta-agonist, use of oral or inhaled steroids within last 3 month
	Baseline characteristics of treatment/control groups: crossover

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Weiner 1999 *(Continued)*

Interventions	BUD 400 µg, 2 times a day (800 µg/d) Placebo 2 times a day Metered dose inhaler via spacer device 6 weeks each treatment period (crossover)
Outcomes	FEV1 Rescue bronchodilator usage
Notes	Second phase of study: inhaled BUD 800 µg 2 times a day versus BUD 400 µg 2 times a day for 6 wk, crossover (not included in this review) Third phase of study: oral prednisolone 40 mg/d versus placebo 6 wk, crossover (not included in this review)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Method not stated
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Weir 1990a

Methods	Design: crossover, 2 weeks washout Randomisation: yes, method not stated Blinding: double blind, double dummy Withdrawals: stated
Participants	Setting: single centre study, hospital outpatient clinic Number eligible: not stated Number enrolled: 127 Number in treatment group: 127 Number in control group: 127 Number of withdrawals (treatment/control): 20 withdrawals

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Weir 1990a *(Continued)*

	Number completing trial (treatment/control): 107 (crossover) Age range: mean 62.9 yr (SD 9.0) Sex: 82M, 25F Ethnicity: not stated COPD diagnosis: adult onset chronic airflow obstruction of at least 5 yr duration and FEV1<70% predicted Severity of COPD: mean FEV1 44.2% predicted Inclusion criteria: as above, 95/107 were current or ex-smokers Exclusion criteria: asthma, respiratory symptoms in childhood, variability in symptoms except in association with infections, acute attacks of wheezing and breathlessness, deterioration after exposure to specific allergens, use of oral or inhaled steroids in previous 6 month Baseline characteristics of treatment/control groups: crossover
Interventions	BDP 500 µg, 3 times a day (1500 µg/d) Placebo 3 times a day metered-dose inhaler 2 weeks each treatment period (crossover)
Outcomes	Spirometry Mean PEFR TLCO Serum IgE levels
Notes	Significant order effect was observed: data included here are from the first treatment period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Method not stated
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind, double dummy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar withdrawals in both arms
Selective reporting (reporting bias)	Low risk	All outcomes reported

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Weir 1999

Methods	Design: parallel group Randomisation: yes, method not stated Blinding: double blind, double dummy Withdrawals: stated
Participants	Setting: multicentre study, UK, hospital outpatient clinic Number eligible: not stated Number enrolled: 98 Number in treatment group: 49 Number in control group: 49 Number of withdrawals (treatment/control): 39 total Number completing trial (treatment/control): 59 total Age range: adult (mean 65.5 yr in intervention group, 67.6 yr in control group Sex: 73M, 15F Ethnicity: not stated COPD diagnosis: clinical diagnosis of COPD, adult onset airflow obstruction , FEV1 <70% predicted, FEV1/FVC <65% Severity of COPD: Mean pre-bronchodilator FEV1 39.7% in intervention group, 41.4% in control group Inclusion criteria: as for COPD diagnosis Exclusion criteria: clinical diagnosis of asthma (including clinical significant bronchodilator reversibility, acute attacks of breathlessness with recovery between attacks), significant improvement with steroid treatment in the past, steroid treatment clinically indicated, use of steroids >3 month in last 1 yr or during last 4 wk Baseline characteristics of treatment/control groups: more females in the intervention group
Interventions	BDP 750 µg, 2 times a day (1500 µg/d) for weight <50 kg, BDP 1000 µg, 2 times a day (2000 µg/d) for weight >50 kg Placebo 2 times a day Metered dose inhaler (identical) via spacer device 2 years
Outcomes	Change in pre-bronchodilator FEV1 Change in pre-bronchodilator FVC Change in post-bronchodilator FEV1 Change in post-bronchodilator FVC PC20 histamine Exacerbations Dyspnoea index CRQ (subgroup)
Notes	

Risk of bias

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Weir 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Method not stated
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Low risk	All outcomes reported

Wempe 1992

Methods	Design: crossover, no washout
	Randomisation: yes, method not stated
	Blinding: double blind, double dummy
	Withdrawals: stated
Participants	Setting: single centre study
	Number eligible: not stated
	Number enrolled: 10
	Number in treatment group: 10 (crossover)
	Number in control group: 10 (crossover)
	Number of withdrawals (treatment/control): 2 in total
	Number completing trial (treatment/control): 8 in total
	Age range: 49 to 66 yr
	Sex: 8M, 2F
	Ethnicity: not stated
	COPD diagnosis: dyspnoea continuously or on exertion, with BHR
	Severity of COPD: FEV1 % predicted range 44 to 79%
	Inclusion criteria: current or former smokers, FEV1 40 to 80% predicted, PC20 to histamine <8 mg/ml
	Exclusion criteria: asthma, respiratory infection or exacerbation in previous 2 months, positive skin prick tests, elevated total IgE
	Baseline characteristics of treatment/control groups: comparable

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Wempe 1992 *(Continued)*

Interventions	BUD 1,600 µg/d Prednisolone 40 mg daily Placebo Metered-dose inhaler with spacing device 3 weeks each treatment period (crossover study)
Outcomes	FEV1 response to cumulative doubling doses of bronchodilators
Notes	4 study days after each treatment period; no actual washout; no carry-over effects observed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Method not stated
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Yildiz 2004

Methods	Design: parallel group Randomisation: yes, method not stated Blinding: double blind Withdrawals: Stated
Participants	Setting: single centre study, hospital outpatient clinic Number eligible: 38 Number enrolled: 38 Number in treatment group: 20 Number in control group: 18 Number of withdrawals (treatment/control): 0/0 Number completing trial (treatment/control): 20/18 Age range: 67yr 8.2Y Sex: 38M 0F Ethnicity: Not stated

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Yildiz 2004 *(Continued)*

	COPD diagnosis: GOLD II (Prebronchodilator FEV1 30-80% of predicted, FEV1/FVC <70% of predicted Severity of COPD: ICS: 51% 22 predicted; P: 40% 14 predicted Inclusion criteria: Irreversible airway obstruction <10% improvement in FEV1 post-bronchodilator, Smoking history of >20 pack years, no exacerbation of respiratory tract infection in previous 4 weeks Exclusion criteria: Asthma, clinical signs of right heart failure, recent hospitalisation or admission to emergency department because of exacerbation, requirement for regular use of oxygen therapy, had used inhaled or oral ICS in the last 6 weeks Baseline characteristics of treatment/control groups: comparable
Interventions	BUD 800µg, 1 time a day (800µg/d) Placebo Both groups received combined bronchodilator therapy: Formoterol + Ipratropium bromide
Outcomes	St Georges Respiratory Questionnaire Score FEV1 FVC FEV1/FVC PaO2 PaCO2 SaO2
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Method not stated
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported

Abbreviations:
ATS: American Thoracic Society; bd: twice a day; BAL: bronchoalveolar lavage; BDP: beclomethasone dipropionate; BHR: bronchial hyper-responsiveness; BUD: budesonide; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; CRQ: Chronic Respiratory Questionnaire; CT: computed tomography; DPI: dry powder inhaler; Dx: diagnosis; ECP: Eosinophil Cationic Protein; eNO: exhaled nitric oxide; FEV1: forced expiratory volume in one second; FP: fluticasone propionate; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease; HRQL: health-related quality of life; Hx: History; ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; LTOT: long-term oxygen therapy; MF: mometasone furoate; MMEFR: maximal mid-expiratory flow rate; MRC: Medical Research Council; OCS: oral corticosteroids; PC20 MCh: Methacholine challenge test; PEFR: peak expiratory flow rate; pMDI pressurised metered dose inhaler; qd: quaque die, a Latin phrase meaning "every day"; QOL: quality of life; RCT: randomised controlled trial; RTI: respiratory infection; SABA: short-acting beta$_2$-agonist; SAE: serious adverse event; SD: standard deviation; SFC: salmeterol/fluticasone propionate; SGRQ: St George's Respiratory Questionnaire; RTI: respiratory tract infection; RV: residual volume; TAA: triamcinolone acetonide; TLC: total lung capacity; VAS: visual analogue scale; VC: vital capacity; vs: versus

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albers 2004	Excluded: subjects had rapid decline in lung function, who were at risk of COPD
Anonymous 1999	Excluded: summary of RCT (Pauwels 1999), not original RCT
Anonymous 2000	Excluded: review, not a clinical trial
Balbi 2000	Excluded: Open trial of BDP in COPD examining bronchoalveolar lavage parameters, not RCT
Bensch 2003	Excluded: asthma
Burge 1999	Excluded: letter referring to a previous RCT (Burge, in: Bronchitis V. Postma DS and Gerritsen J, eds. 1994)
Chan 1993	Excluded: not randomised; randomisation was changed without notifying the chief investigators. Double-blind, placebo controlled crossover trial of BUD 1600 µg/day versus placebo in 20 COPD patients; All patients received placebo for 4 weeks, then BUD for 8 weeks, without a washout period between placebo and BUD.
Confalonieri 1998	Excluded: open trial of BDP versus no treatment, not double-blind. Randomised, parallel-group trial of BDP 500 µg 3 times a day versus no treatment for 2 months in 34 COPD patients. Markers of airway inflammation measured in induced sputum
Corda 2008	Excluded: focused on alpha-1 antitrypsin deficiency patients only
Cox 1999	Excluded: RCT of BDP versus placebo in smokers with normal FEV1 (> 70% predicted), not COPD with airflow obstruction
Dompeling 1992	Excluded: trial of adding BDP to bronchodilators in asthma or COPD patients, not RCT of ICS versus placebo
Dompeling 1993	Excluded: trial of adding BDP to bronchodilators in asthma or COPD patients, not RCT of ICS versus placebo
Egan 1999	Excluded: bone density study in asthmatics
Engel 1989	Excluded: RCT of BUD in smokers with chronic bronchitis and BHR to histamine; mostly normal lung function; not COPD patients with airflow obstruction
Fattore 2005	Excluded: cost analysis
Fazio 1986	Excluded: Single dose, double-blind study of BDP in patients with COPD. 5 received BDP, 5 received placebo. Mucociliary clearance measured, no other outcomes
Guleria 2003	Excluded: single inhalation study
Keatings 1997	Excluded: sequential single blind, 2 week crossover study of BUD in COPD patients, with double-blind assessment of inflammatory markers. Demonstrated no improvement in lung function, symptom scores or inflammatory indices.
Kozak-Skzopek 1997	Excluded: English title - "Inhaled budesonide therapy for chronic bronchitis". Double-blind study, no randomisation described. Intervention: BUD 200 µg, 3 times per day. Authors did not respond when contacted regarding randomisation.

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Study	Reason for exclusion
Matlin 1976	Abstract only: Results reported were: 17 patients with COPD were treated in a double-blind, crossover study with triamcinolone 800 mcg/day versus placebo for 2 weeks in random sequence. 6 of the 17 patients had at least a 40% increase of FEV1 on triamcinolone whereas the maximum increase with placebo was 33%. Presented at American Thoracic Society meeting 1976. No subsequent publication. Author not contactable.
Melani 1999	Excluded: nebuliser used to deliver ICS. Randomised, double-blind cross-over study of 20 severe COPD patients, nebulised BDP 2 mg bd versus placebo for 4 weeks.
Moller 1999	Excluded: case series, not RCT (translated from German)
Nava 2000	Excluded: RCT of FP versus placebo in ventilator-dependent COPD patients, 5 days duration, crossover, FEV1 performed through tracheostomy (information provided by first author)
Nishimura 2000	Excluded: oral corticosteroids added to inhaled corticosteroids, not RCT of inhaled corticosteroids versus placebo
O'Brien 2001	Excluded: withdrawal study
Ouyang 1998	Excluded: (English abstract): single-blind trial, not double-blind. Randomised, placebo-controlled trial of BDP 1000 µg daily for 6 week in 61 stable non-asthmatic COPD patients.
Roth 1996	Excluded: Review of study by G Eichler, "Inhaled corticosteroids are effective and well tolerated". Not placebo-controlled. Open, multicentre, randomised study of 1 mg flunisolide versus 800 µg BUD for 12 weeks in COPD patients. Limited data reported. (Translated from German)
Sandrini 2003	Excluded: withdrawal study
Sapey 2000	Excluded: review, not a clinical trial
Schuurmans 2001	Excluded: review, not a clinical trial (translated from German)
Spicuzza 2004	Excluded: acute study
Tsang 1999	Excluded: letter referring to a previous RCT in bronchiectasis
Turker 2004	Excluded: add on of theophylline
van den Boom 2001	Excluded: cost analysis in obstructive airways disease
van der Valk 2002	Excluded: withdrawal study
van Grunsven 2000	RCT of FP versus placebo in subjects with "early COPD" (FEV1 decline of >0.04L/yr), not patients with airflow limitation
van Schayck 1995	Excluded: trial of adding BDP to bronchodilators in COPD, not RCT of ICS versus placebo
Vestbo 2000	Excluded: translation of Vestbo 1999 (Lancet; 353(9167):1819-23) (Translated from Danish)
Watson 1992	Excluded: RCT of BUD versus placebo in 14 smokers with BHR to histamine and mild airways obstruction; most subjects had normal spirometry, not COPD patients with airflow limitation
Weiner 1997	Excluded: (abstract): subgroup of COPD patients who were responders to beta-agonist, reported in Weiner 1999 (Journal of Internal Medicine 1999;245(1):83-9)
Weir 1993	Excluded: single blind trial of BDP at different doses versus placebo, not double-blind

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Study	Reason for exclusion
Wesseling 1991	Excluded: RCT of BUD versus placebo in chronic bronchitis patients with FEV1 % pred >=70% (mean 96%, SD 17%), not COPD with airflow obstruction
Whittaker 2000	Excluded: review, not a clinical trial
Wilcke 1997	Excluded: RCT of BUD versus placebo in alpha1-antitrypsin deficiency patients
Williamson 2009	Excluded: Randomised crossover study of two doses of FP vs placebo
Yildiz 2000	Excluded: Information from first author - single blinded study, not double-blinded (clinician aware of treatment allocation; patient and differential cell count technician not aware). Randomised trial of FP 500 µg 3 times a day vs placebo for 2 months in 18 COPD patients.

bd: twice a day; BDP: beclomethasone dipropionate; BHR: bronchial hyper-responsiveness; BUD: budesonide; COPD: chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Questionnaire; FEV1: forced expiratory volume in one second; FP: fluticasone propionate; ICS: inhaled corticosteroids; OCS: oral steroids; RCT: randomised controlled trial; SABAs: short-acting beta-agonists; SD: standard deviation

DATA AND ANALYSES

Comparison 1. ICS versus placebo, parallel-group studies, greater than 6 months (all doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post-bronchodilator FEV1 - Rate of decline	5	2333	mL/year (Fixed, 95% CI)	5.80 [-0.28, 11.88]
1.1 Less than 1000 µg BDP equivalent/day	3	1486	mL/year (Fixed, 95% CI)	3.76 [-3.43, 10.95]
1.2 Greater than 1000 µg BDP equivalent/day	2	847	mL/year (Fixed, 95% CI)	10.91 [-0.47, 22.29]
2 Change in post-bronchodilator FEV1 (mL/yr)	5	4823	Mean Difference (IV, Random, 95% CI)	6.88 [1.80, 11.96]
2.1 Less than 1000 µg BDP equivalent/day	3	1542	Mean Difference (IV, Random, 95% CI)	1.71 [-5.66, 9.07]
2.2 Greater than 1000 µg BDP equivalent/day	2	3281	Mean Difference (IV, Random, 95% CI)	11.58 [4.57, 18.60]
3 FEV1 (% change from baseline)	1		% (Fixed, 95% CI)	Totals not selected
3.1 Less than 1000 µg BDP equivalent/day	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Greater than 1000 µg BDP equivalent/day	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Total number of deaths	9	8390	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Study duration 1 year	4	1907	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.33, 1.31]
4.2 Study duration 2 or more years	5	6483	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.20]
5 Exacerbation rate	5	2586	Exn's/pt/yr (Fixed, 95% CI)	-0.26 [-0.37, -0.14]
5.1 Less than 1000 µg BDP equivalent/day	0	0	Exn's/pt/yr (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Greater than 1000 µg BDP equivalent/day	5	2586	Exn's/pt/yr (Fixed, 95% CI)	-0.26 [-0.37, -0.14]
6 Exacerbation rate (no. per patient per yr)	5	2253	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.08]
6.1 Less than 1000 µg BDP equivalent/day	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Greater than 1000 µg BDP equivalent/day	5	2253	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.08]
7 Exacerbation rate - stratified by analysis approach	5	2586	Exn's/pt/yr (Fixed, 95% CI)	-0.26 [-0.37, -0.14]
7.1 Unweighted analysis	2	925	Exn's/pt/yr (Fixed, 95% CI)	-0.29 [-0.52, -0.05]
7.2 Weighted analysis	3	1661	Exn's/pt/yr (Fixed, 95% CI)	-0.25 [-0.38, -0.12]
8 No. of patients with at least one exacerbation	4	2347	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.70, 0.98]
8.1 Less than 1000 µg BDP equivalent/day	2	857	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.67, 1.16]
8.2 Greater than 1000 µg BDP equivalent/day	3	1490	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.65, 0.98]
9 Change in SGRQ total score (units/yr)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Less than 1000 µg BDP equivalent/day	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Greater than 1000 µg BDP equivalent/day	2	1335	Mean Difference (IV, Random, 95% CI)	-1.17 [-2.00, -0.34]
10 Mean change in SGRQ - total scores	5	2507	Units on SGRQ scale (Fixed, 95% CI)	-1.22 [-1.83, -0.60]
10.1 Less than 1000 µg BDP equivalent/day	0	0	Units on SGRQ scale (Fixed, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Greater than 1000 µg BDP equivalent/day	5	2507	Units on SGRQ scale (Fixed, 95% CI)	-1.22 [-1.83, -0.60]
11 Total SGRQ score (units)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Cough score	3	739	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.14, 0.02]
12.1 Less than 1000 µg BDP equivalent/day	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Greater than 1000 µg BDP equivalent/day	3	739	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.14, 0.02]
13 Breathlessness score	3	739	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.16, 0.00]
13.1 Less than 1000 µg BDP equivalent/day	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Greater than 1000 µg BDP equivalent/day	3	739	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.16, 0.00]
14 Throat irritation (no. of patients)	2	1855	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.68, 1.41]
14.1 Less than 1000 µg BDP equivalent/day	1	1113	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.30, 0.89]
14.2 Greater than 1000 µg BDP equivalent/day	1	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [1.01, 2.69]
15 Oropharyngeal candidiasis (no. of patients)	6	5586	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.65 [2.03, 3.46]
15.1 Less than 1000 µg BDP equivalent/day	4	3506	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.94 [1.93, 4.46]
15.2 Greater than 1000 µg BDP equivalent/day	3	2080	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.47 [1.74, 3.49]
16 Hoarseness or dysphonia (no. of patients)	4	3267	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [1.41, 2.70]
16.1 Less than 1000 µg BDP equivalent/day	2	1790	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [1.16, 2.84]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Greater than 1000 µg BDP equivalent/day	2	1477	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [1.32, 3.36]
17 Bruising (no. of patients)	5	5073	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [1.31, 2.03]
17.1 Less than 1000 µg BDP equivalent/day	3	2993	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [1.38, 2.52]
17.2 Greater than 1000 µg BDP equivalent/day	3	2080	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [1.03, 1.93]
18 Vertebral fractures (no. of patients)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
18.1 Less than 1000 µg BDP equivalent/day	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Greater than 1000 µg BDP equivalent/day	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Cataracts (no. of patients)	3	1949	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.79, 1.35]
19.1 Less than 1000 µg BDP equivalent/day	1	1113	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.81, 1.44]
19.2 Greater than 1000 µg BDP equivalent/day	2	836	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.34, 1.58]
20 No. of patients with serum cortisol below normal range at any time	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
20.1 Less than 1000 µg BDP equivalent/day	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Greater than 1000 µg BDP equivalent/day	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Any fractures (no. of patients)	4	5226	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.32]
21.1 Less than 1000 µg BDP equivalent/day	1	653	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.41, 7.28]
21.2 Greater than 1000 µg BDP equivalent/day	3	4573	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.30]
22 Sputum production score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
22.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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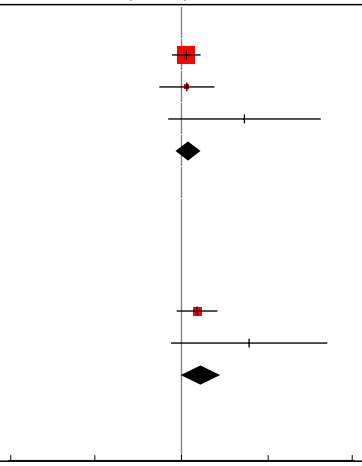
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23 Sputum colour score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
23.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
24 No. of patients with change from within to below normal for serum cortisol	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
24.1 Less than 1000 µg BDP equivalent/day	0		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24.2 Greater than 1000 µg BDP equivalent/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25 Pneumonia	7	6235	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [1.30, 1.86]
25.1 Less than 1000 µg BDP equivalent/day	2	803	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.43, 1.45]
25.2 Greater than 1000 µg BDP equivalent/day	5	5432	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [1.38, 2.00]

Analysis 1.1. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 1 Post-bronchodilator FEV1 - Rate of decline.

Study or subgroup	ICS N	Placebo N	mL/year (SE)	mL/year IV, Fixed, 95% CI	Weight	mL/year IV, Fixed, 95% CI
1.1.1 Less than 1000 µg BDP equivalent/day						
LHS 2000	553	545	2.8 (4.184)		54.95%	2.8[-5.4,11]
Vestbo 1999	145	145	3.1 (8.112)		14.61%	3.1[-12.8,19]
Weir 1999	49	49	36.3 (22.45)		1.91%	36.3[-7.7,80.3]
Subtotal (95% CI)					**71.47%**	**3.76[-3.43,10.95]**
Heterogeneity: Tau^2=0; Chi^2=2.16, df=2(P=0.34); I^2=7.41%						
Test for overall effect: Z=1.02(P=0.31)						
1.1.2 Greater than 1000 µg BDP equivalent/day						
Burge 2000	339	325	9 (6)		26.71%	9[-2.76,20.76]
van Grunsven 1999	95	88	39 (23)		1.82%	39[-6.08,84.08]
Subtotal (95% CI)					**28.53%**	**10.91[-0.47,22.29]**
Heterogeneity: Tau^2=0; Chi^2=1.59, df=1(P=0.21); I^2=37.22%						
Test for overall effect: Z=1.88(P=0.06)						



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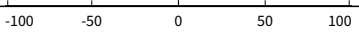
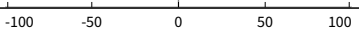
Study or subgroup	ICS N	Placebo N	mL/year (SE)	mL/year IV, Fixed, 95% CI	Weight	mL/year IV, Fixed, 95% CI
Total (95% CI)					**100%**	**5.8[-0.28,11.88]**
Heterogeneity: Tau²=0; Chi²=4.84, df=4(P=0.3); I²=17.33%						
Test for overall effect: Z=1.87(P=0.06)						
Test for subgroup differences: Chi²=1.09, df=1 (P=0.3), I²=7.89%						



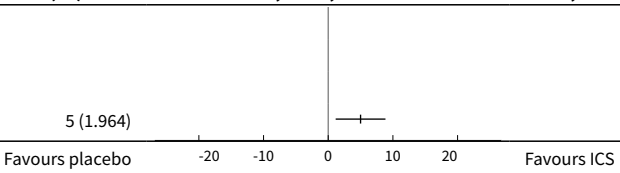
Analysis 1.2. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 2 Change in post-bronchodilator FEV1 (mL/yr).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 Less than 1000 µg BDP equivalent/day							
LHS 2000	553	-44 (76.2)	545	-45.9 (77.6)		31.17%	1.9[-7.2,11]
Schermer 2009	94	-59 (55.3)	96	-60 (52.9)		10.89%	1[-14.39,16.39]
Shaker 2009	127	-54 (83.4)	127	-56 (92)		5.53%	2[-19.59,23.59]
Subtotal ***	**774**		**768**			**47.6%**	**1.71[-5.66,9.07]**
Heterogeneity: Tau²=0; Chi²=0.01, df=2(P=0.99); I²=0%							
Test for overall effect: Z=0.45(P=0.65)							
1.2.2 Greater than 1000 µg BDP equivalent/day							
Burge 2000	339	-50 (75.5)	325	-59 (79.3)		18.57%	9[-2.79,20.79]
Calverley 2007	1356	-42.3 (114.2)	1261	-55.3 (113.6)		33.84%	13[4.27,21.73]
Subtotal ***	**1695**		**1586**			**52.4%**	**11.58[4.57,18.6]**
Heterogeneity: Tau²=0; Chi²=0.29, df=1(P=0.59); I²=0%							
Test for overall effect: Z=3.24(P=0)							
Total ***	**2469**		**2354**			**100%**	**6.88[1.8,11.96]**
Heterogeneity: Tau²=0; Chi²=3.92, df=4(P=0.42); I²=0%							
Test for overall effect: Z=2.66(P=0.01)							
Test for subgroup differences: Chi²=3.62, df=1 (P=0.06), I²=72.4%							



Analysis 1.3. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 3 FEV1 (% change from baseline).

Study or subgroup	Steroids N	Placebo N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
1.3.1 Less than 1000 µg BDP equivalent/day					
1.3.2 Greater than 1000 µg BDP equivalent/day					
Szafranski 2003	1	1	5 (1.964)		5[1.15,8.85]



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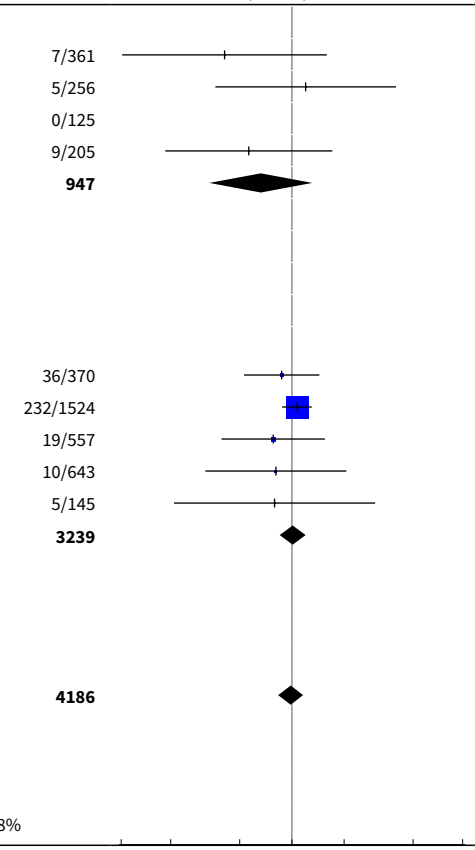
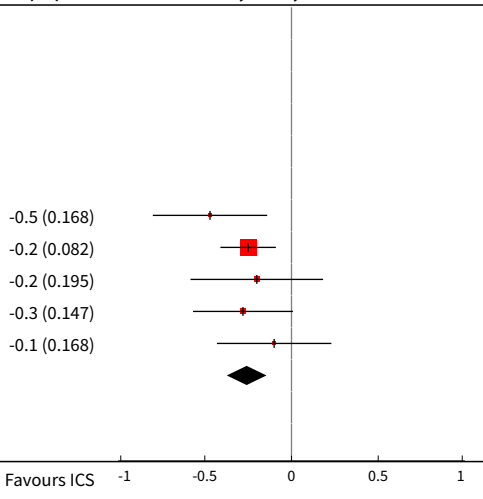
Analysis 1.4. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 4 Total number of deaths.

Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Study duration 1 year					
Calverley 2003a	3/374	7/361		2.51%	0.41[0.1,1.59]
Calverley 2003b	6/257	5/256		1.73%	1.2[0.36,3.98]
SCO30002 2005	0/131	0/125			Not estimable
Szafranski 2003	5/198	9/205		3.06%	0.56[0.19,1.71]
Subtotal (95% CI)	**960**	**947**		**7.3%**	**0.66[0.33,1.31]**
Total events: 14 (ICS), 21 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.51, df=2(P=0.47); I²=0%					
Test for overall effect: Z=1.18(P=0.24)					
1.4.2 Study duration 2 or more years					
Burge 2000	32/372	36/370		11.7%	0.87[0.53,1.44]
Calverley 2007	247/1534	232/1524		69.24%	1.07[0.88,1.3]
LHS 2000	15/559	19/557		6.57%	0.78[0.39,1.55]
Pauwels 1999	8/634	10/643		3.48%	0.81[0.32,2.06]
Vestbo 1999	4/145	5/145		1.72%	0.79[0.21,3.02]
Subtotal (95% CI)	**3244**	**3239**		**92.7%**	**1.01[0.85,1.2]**
Total events: 306 (ICS), 302 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.53, df=4(P=0.82); I²=0%					
Test for overall effect: Z=0.1(P=0.92)					
Total (95% CI)	**4204**	**4186**		**100%**	**0.98[0.83,1.16]**
Total events: 320 (ICS), 323 (Placebo)					
Heterogeneity: Tau²=0; Chi²=4.28, df=7(P=0.75); I²=0%					
Test for overall effect: Z=0.2(P=0.84)					
Test for subgroup differences: Chi²=1.37, df=1 (P=0.24), I²=27.08%					



Analysis 1.5. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 5 Exacerbation rate.

Study or subgroup	ICS N	Placebo N	Exn's/pt/yr (SE)	Exn's/pt/yr IV, Fixed, 95% CI	Weight	Exn's/pt/yr IV, Fixed, 95% CI
1.5.1 Less than 1000 µg BDP equivalent/day						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.2 Greater than 1000 µg BDP equivalent/day						
Burge 2000	372	370	-0.5 (0.168)		12.04%	-0.47[-0.8,-0.14]
Calverley 2003a	374	371	-0.2 (0.082)		51.2%	-0.25[-0.41,-0.09]
Calverley 2003b	257	256	-0.2 (0.195)		8.97%	-0.2[-0.58,0.18]
Szafranski 2003	198	205	-0.3 (0.147)		15.78%	-0.28[-0.57,0.01]
van Grunsven 1999	95	88	-0.1 (0.168)		12.02%	-0.1[-0.43,0.23]
Subtotal (95% CI)					**100%**	**-0.26[-0.37,-0.14]**
Heterogeneity: Tau²=0; Chi²=2.59, df=4(P=0.63); I²=0%						
Test for overall effect: Z=4.43(P<0.0001)						



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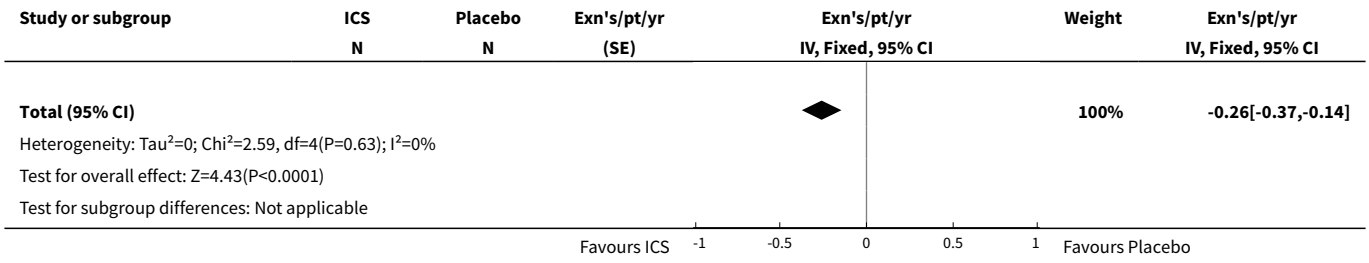
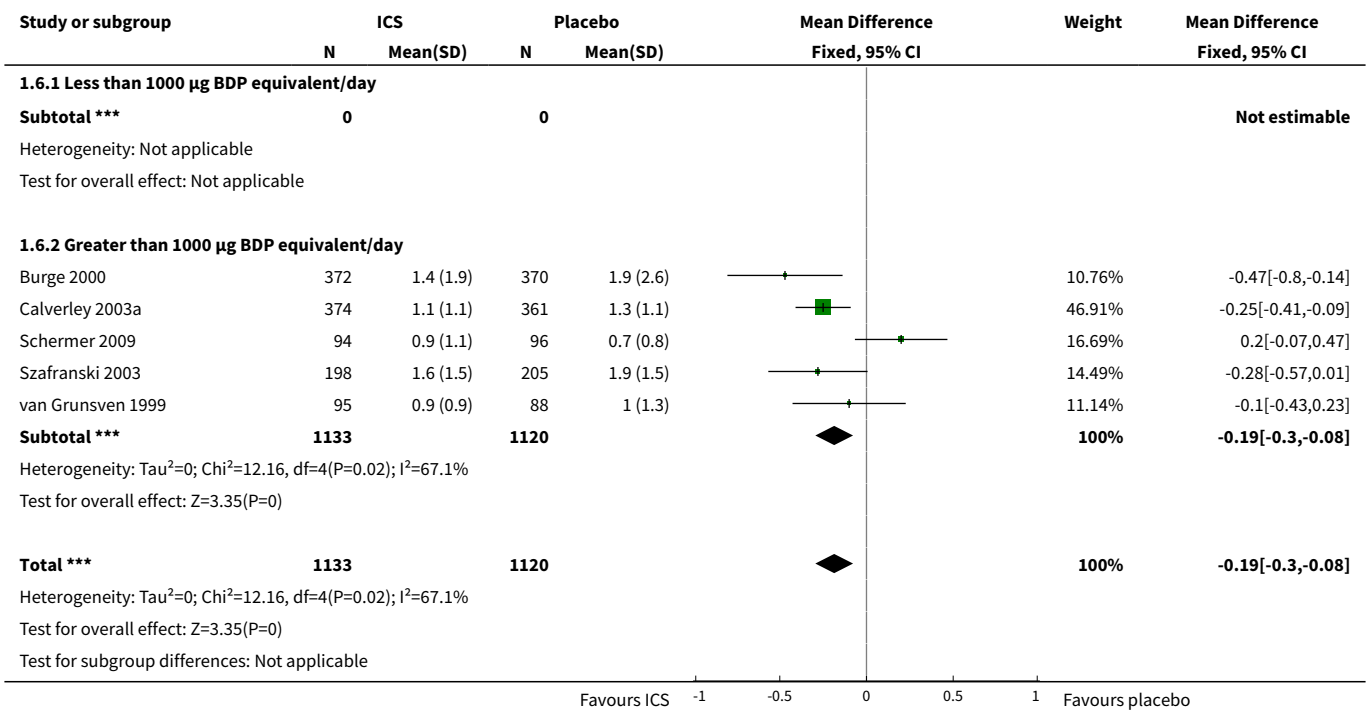
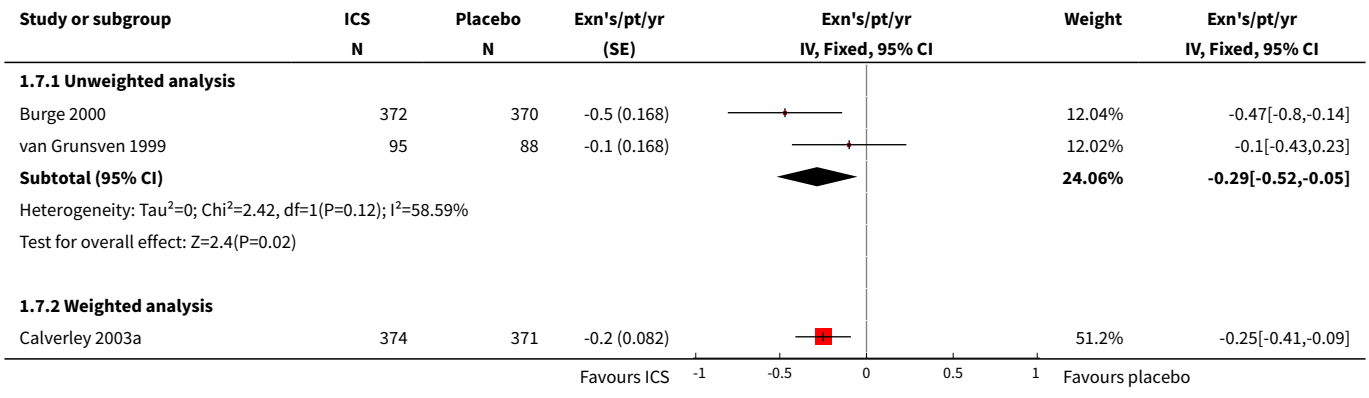


Analysis 1.6. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 6 Exacerbation rate (no. per patient per yr).



Analysis 1.7. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 7 Exacerbation rate - stratified by analysis approach.



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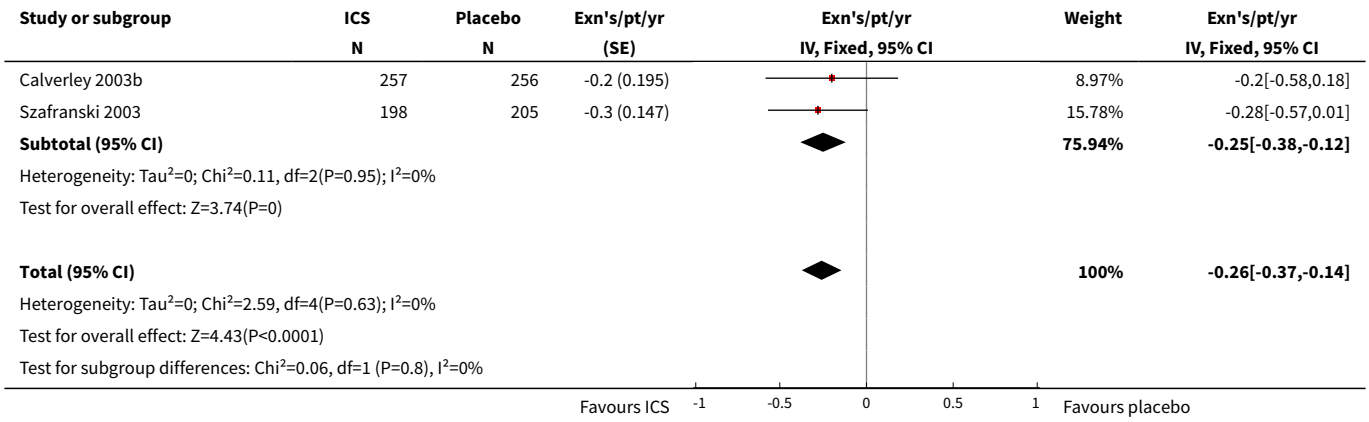
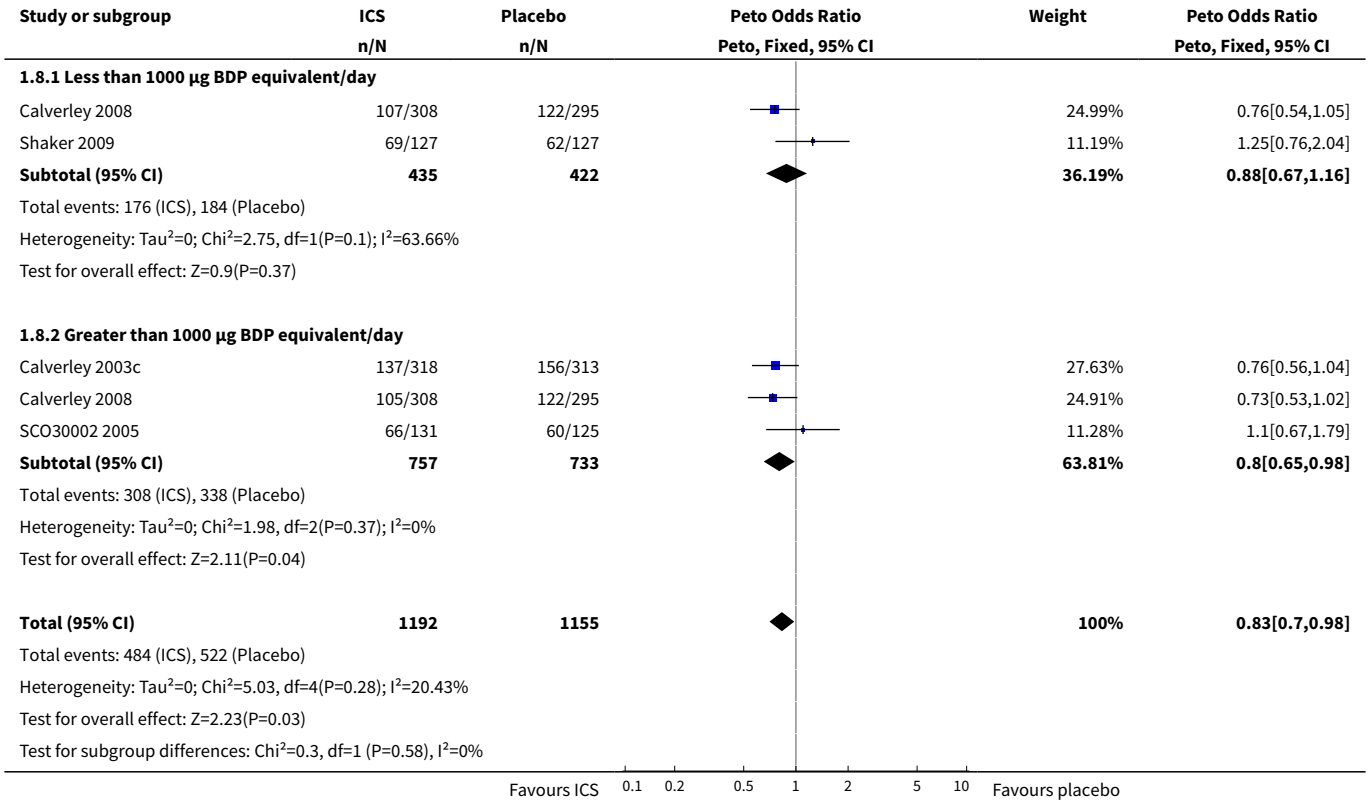
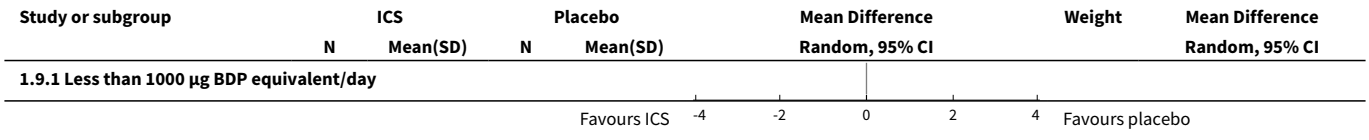


Analysis 1.8. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 8 No. of patients with at least one exacerbation.



Analysis 1.9. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 9 Change in SGRQ total score (units/yr).



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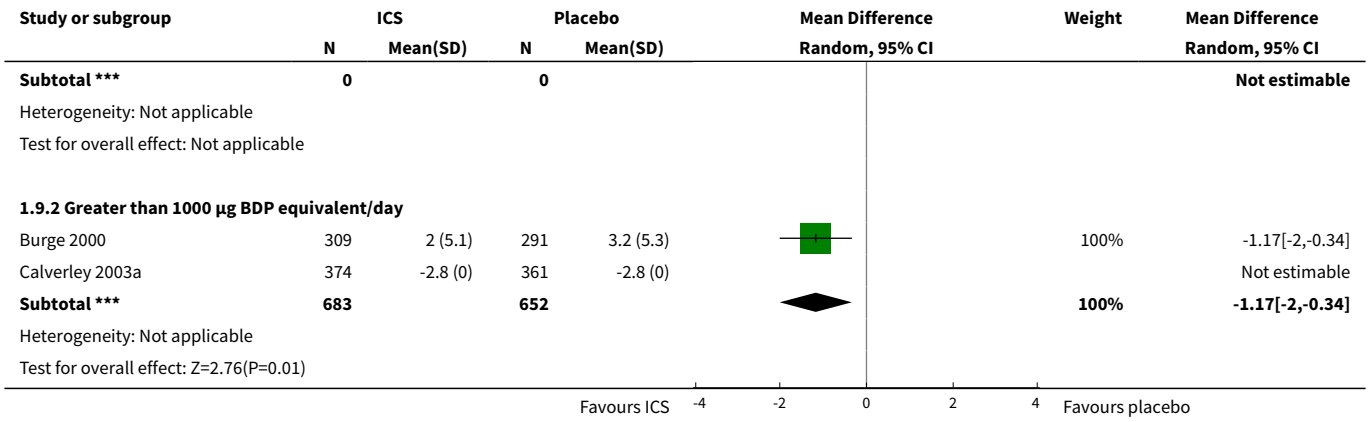
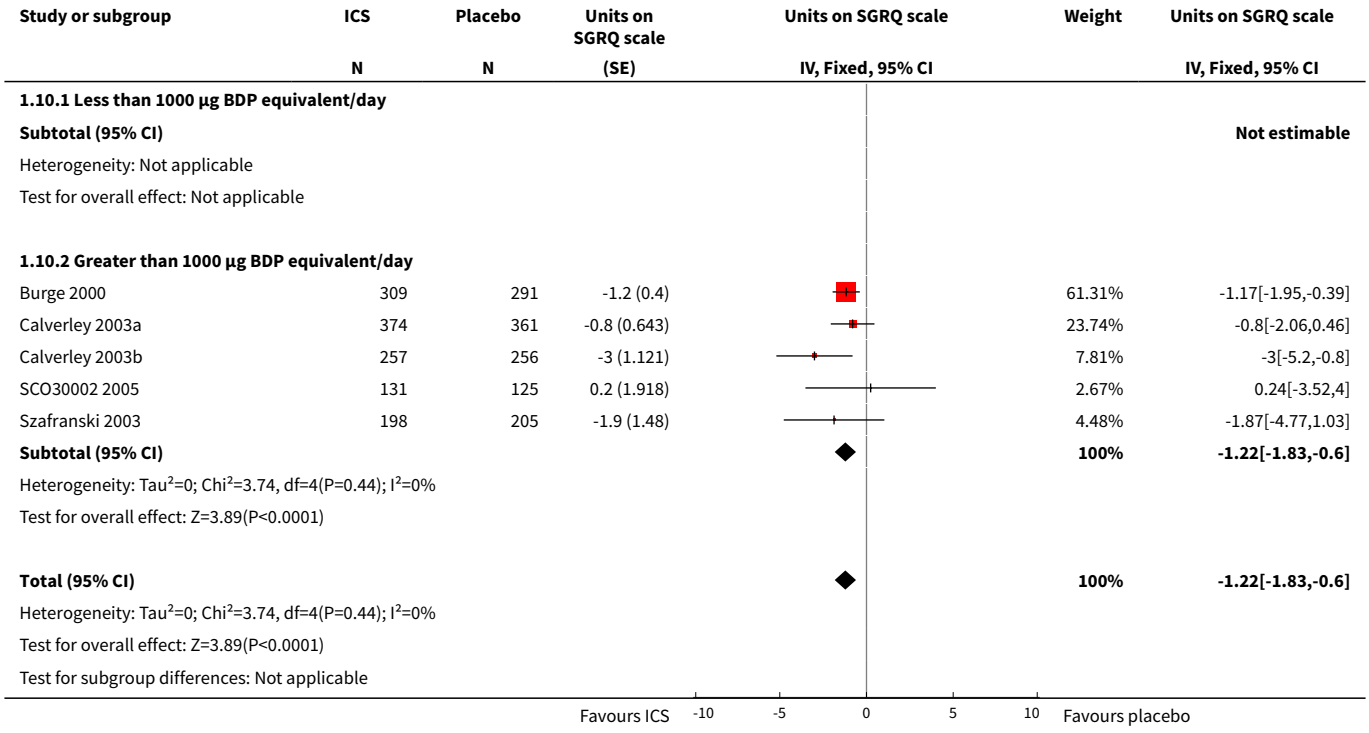
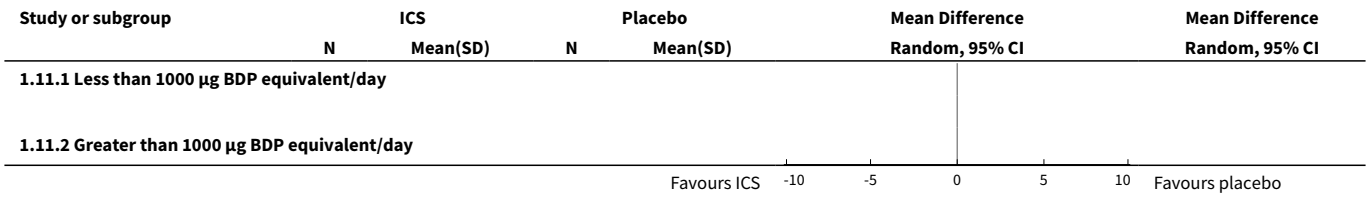


Analysis 1.10. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 10 Mean change in SGRQ - total scores.



Analysis 1.11. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 11 Total SGRQ score (units).



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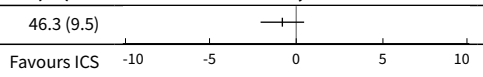
Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Calverley 2003a	374	45.5 (7.7)	361	46.3 (9.5)		-0.8[-2.06,0.46]

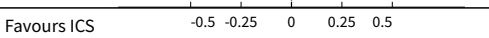


Analysis 1.12. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 12 Cough score.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.12.1 Less than 1000 µg BDP equivalent/day							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.12.2 Greater than 1000 µg BDP equivalent/day							
Calverley 2003a	374	1.4 (0.6)	361	1.4 (0.6)		100%	-0.06[-0.14,0.02]
Calverley 2003b	1	0 (0)	1	0 (0)			Not estimable
Szafranski 2003	1	0 (0)	1	0 (0)			Not estimable
Subtotal ***	**376**		**363**			**100%**	**-0.06[-0.14,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.41(P=0.16)							
Total ***	**376**		**363**			**100%**	**-0.06[-0.14,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.41(P=0.16)							
Test for subgroup differences: Not applicable							

Analysis 1.13. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 13 Breathlessness score.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.13.1 Less than 1000 µg BDP equivalent/day							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.13.2 Greater than 1000 µg BDP equivalent/day							
Calverley 2003a	374	1.6 (0.6)	361	1.7 (0.6)		100%	-0.08[-0.16,0]
Calverley 2003b	1	0 (0)	1	0 (0)			Not estimable
Szafranski 2003	1	0 (0)	1	0 (0)			Not estimable
Subtotal ***	**376**		**363**			**100%**	**-0.08[-0.16,0]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.89(P=0.06)							
Total ***	**376**		**363**			**100%**	**-0.08[-0.16,0]**
Heterogeneity: Not applicable							



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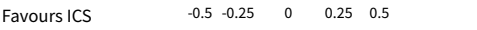
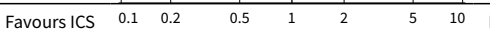
Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=1.89(P=0.06)							
Test for subgroup differences: Not applicable							



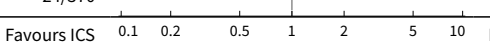
Analysis 1.14. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 14 Throat irritation (no. of patients).

Study or subgroup	ICS n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.14.1 Less than 1000 µg BDP equivalent/day					
LHS 2000	19/558	36/555		45.18%	0.52[0.3,0.89]
Subtotal (95% CI)	**558**	**555**		**45.18%**	**0.52[0.3,0.89]**
Total events: 19 (ICS), 36 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.37(P=0.02)					
1.14.2 Greater than 1000 µg BDP equivalent/day					
Burge 2000	43/372	27/370		54.82%	1.65[1.01,2.69]
Subtotal (95% CI)	**372**	**370**		**54.82%**	**1.65[1.01,2.69]**
Total events: 43 (ICS), 27 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					
Total (95% CI)	**930**	**925**		**100%**	**0.98[0.68,1.41]**
Total events: 62 (ICS), 63 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.54, df=1(P=0); I^2=89.52%					
Test for overall effect: Z=0.12(P=0.9)					
Test for subgroup differences: Chi^2=9.54, df=1 (P=0), I^2=89.52%					



Analysis 1.15. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 15 Oropharyngeal candidiasis (no. of patients).

Study or subgroup	ICS n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.15.1 Less than 1000 µg BDP equivalent/day					
Calverley 2003b	4/257	0/256		1.85%	7.45[1.04,53.18]
Calverley 2008	30/308	10/295		17.37%	2.78[1.47,5.28]
LHS 2000	5/558	2/555		3.23%	2.35[0.53,10.4]
Pauwels 1999	31/634	10/643		18.45%	2.92[1.57,5.44]
Subtotal (95% CI)	**1757**	**1749**		**40.91%**	**2.94[1.93,4.46]**
Total events: 70 (ICS), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.97, df=3(P=0.81); I^2=0%					
Test for overall effect: Z=5.05(P<0.0001)					
1.15.2 Greater than 1000 µg BDP equivalent/day					
Burge 2000	41/372	24/370		27.59%	1.76[1.06,2.93]



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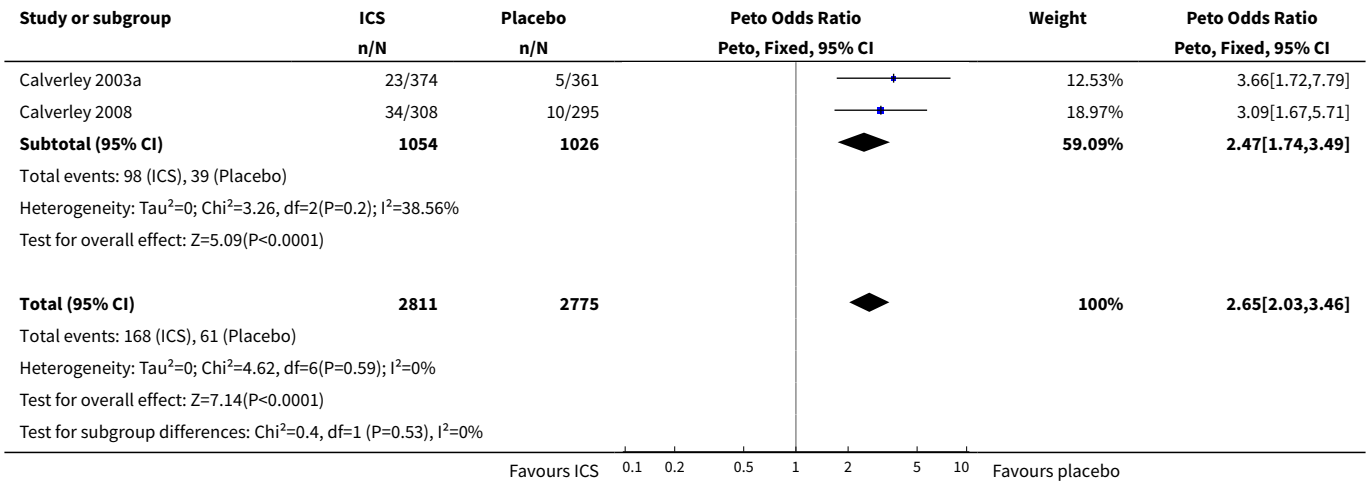
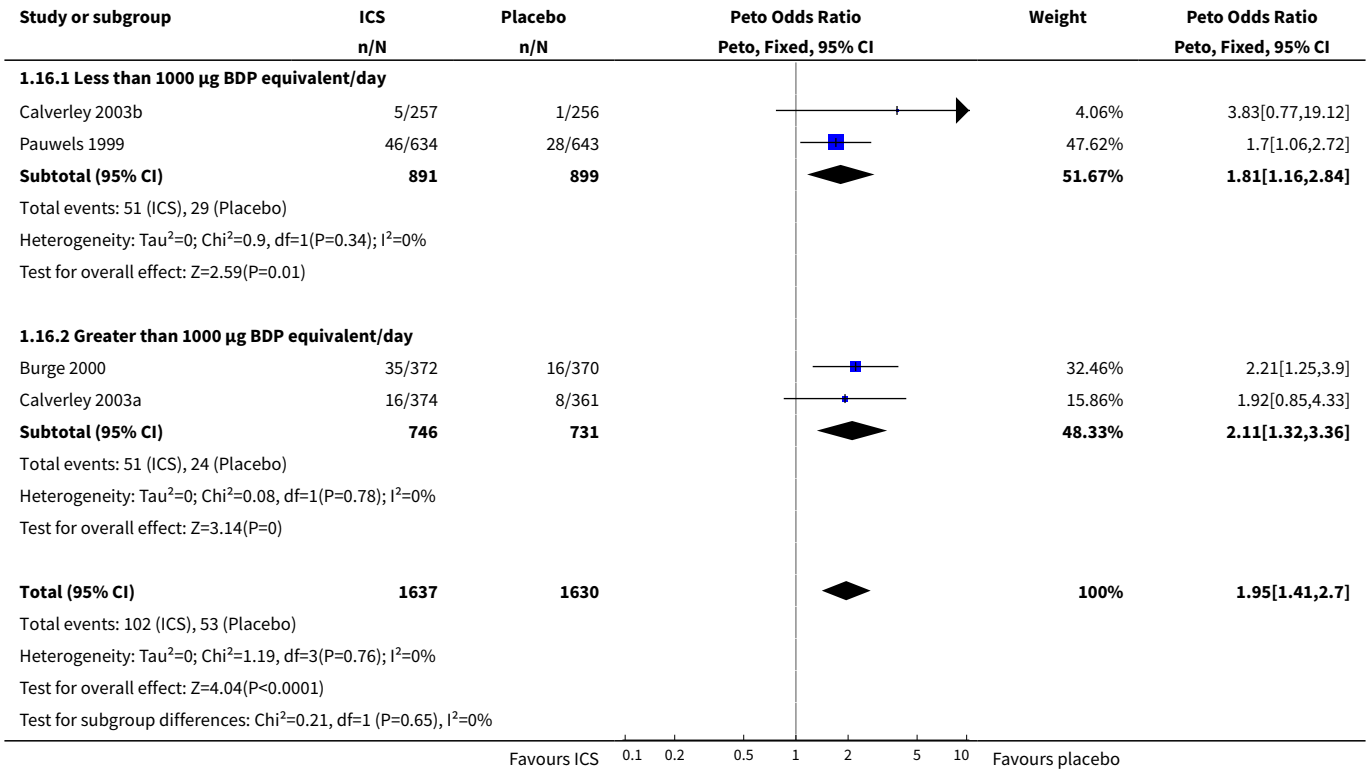


Analysis 1.16. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 16 Hoarseness or dysphonia (no. of patients).



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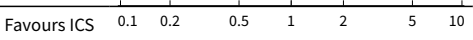
Analysis 1.17. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 17 Bruising (no. of patients).

Study or subgroup	ICS n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.17.1 Less than 1000 µg BDP equivalent/day					
Calverley 2008	45/308	33/295		21.07%	1.35[0.84,2.18]
LHS 2000	12/558	6/555		5.49%	1.96[0.77,4.97]
Pauwels 1999	63/634	27/643		25.94%	2.4[1.56,3.68]
Subtotal (95% CI)	**1500**	**1493**		**52.5%**	**1.87[1.38,2.52]**
Total events: 120 (ICS), 66 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.08, df=2(P=0.21); I^2=34.99%					
Test for overall effect: Z=4.06(P<0.0001)					
1.17.2 Greater than 1000 µg BDP equivalent/day					
Burge 2000	27/372	15/370		12.29%	1.82[0.98,3.39]
Calverley 2003a	26/374	22/361		13.92%	1.15[0.64,2.07]
Calverley 2008	46/308	33/295		21.3%	1.39[0.87,2.23]
Subtotal (95% CI)	**1054**	**1026**		**47.5%**	**1.41[1.03,1.93]**
Total events: 99 (ICS), 70 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.12, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=2.13(P=0.03)					
Total (95% CI)	**2554**	**2519**		**100%**	**1.63[1.31,2.03]**
Total events: 219 (ICS), 136 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.78, df=5(P=0.33); I^2=13.5%					
Test for overall effect: Z=4.41(P<0.0001)					
Test for subgroup differences: Chi^2=1.59, df=1 (P=0.21), I^2=37.04%					

Analysis 1.18. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 18 Vertebral fractures (no. of patients).

Study or subgroup	ICS n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
1.18.1 Less than 1000 µg BDP equivalent/day				
Pauwels 1999	5/634	3/643		1.68[0.42,6.73]
1.18.2 Greater than 1000 µg BDP equivalent/day				



Analysis 1.19. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 19 Cataracts (no. of patients).

Study or subgroup	ICS n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.19.1 Less than 1000 µg BDP equivalent/day					
LHS 2000	122/558	114/555		87.52%	1.08[0.81,1.44]
Subtotal (95% CI)	**558**	**555**		**87.52%**	**1.08[0.81,1.44]**

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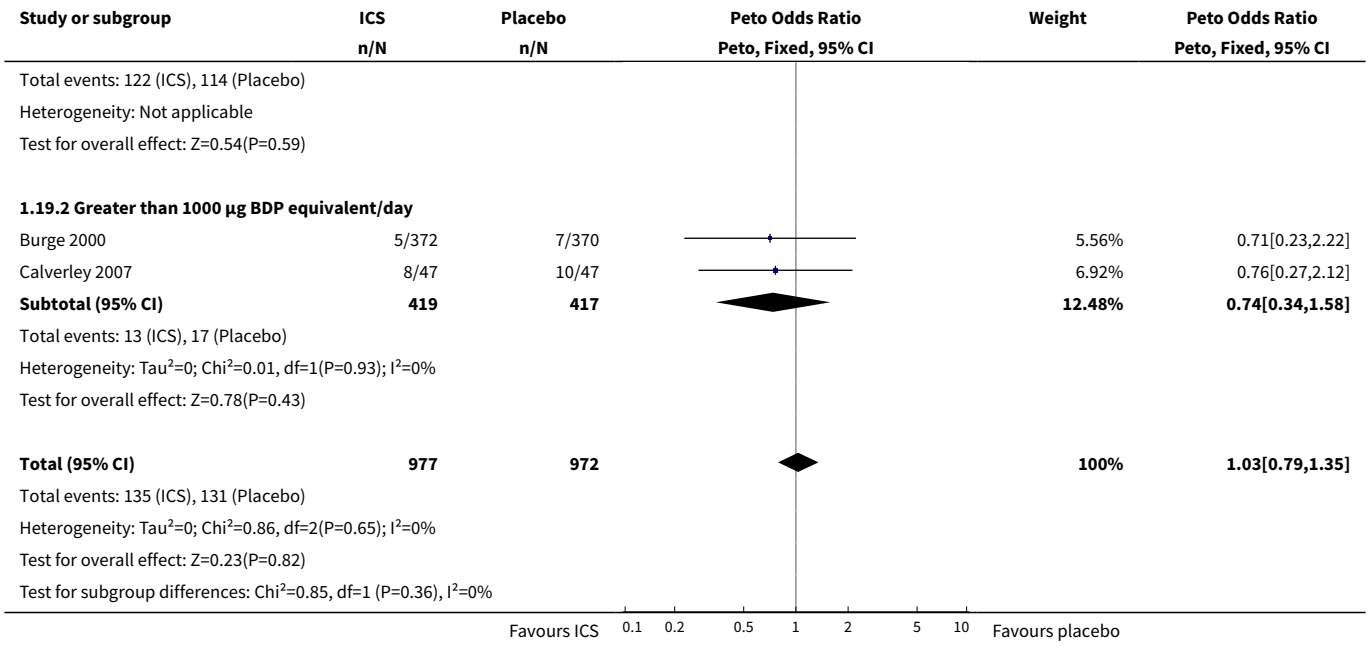
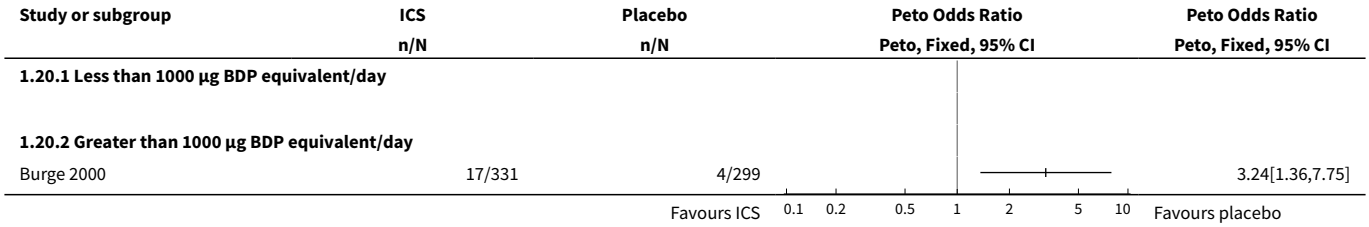
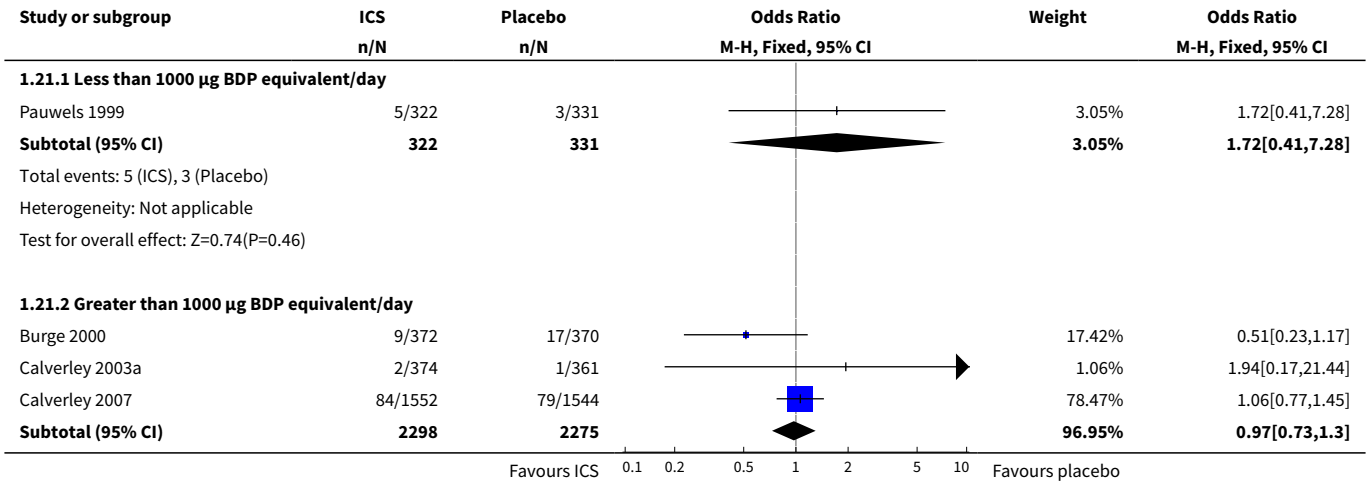


Analysis 1.20. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 20 No. of patients with serum cortisol below normal range at any time.



Analysis 1.21. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 21 Any fractures (no. of patients).



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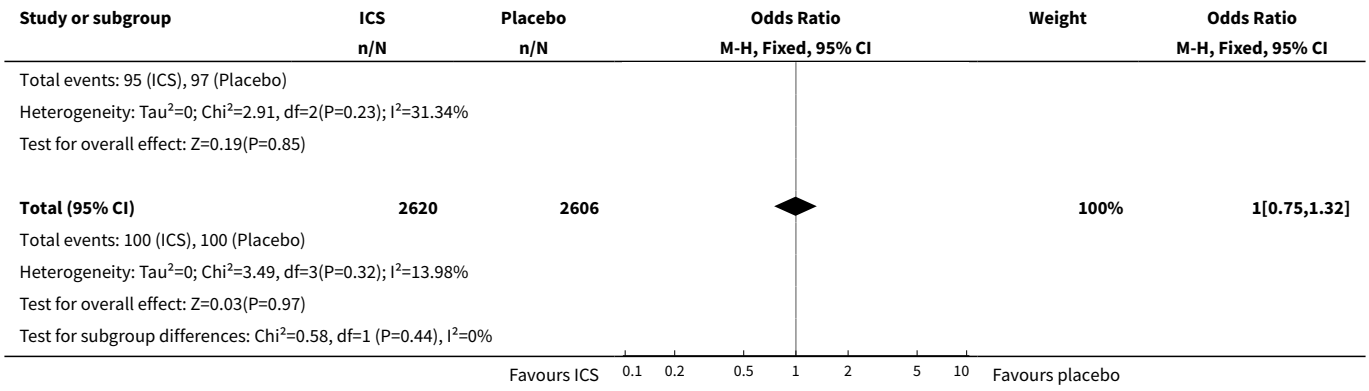
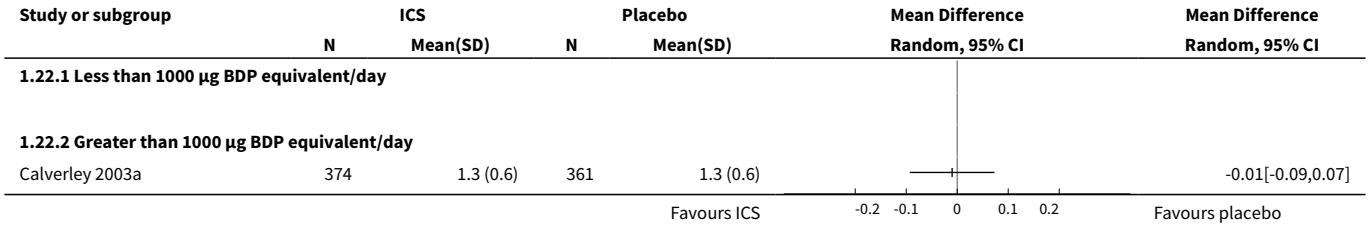
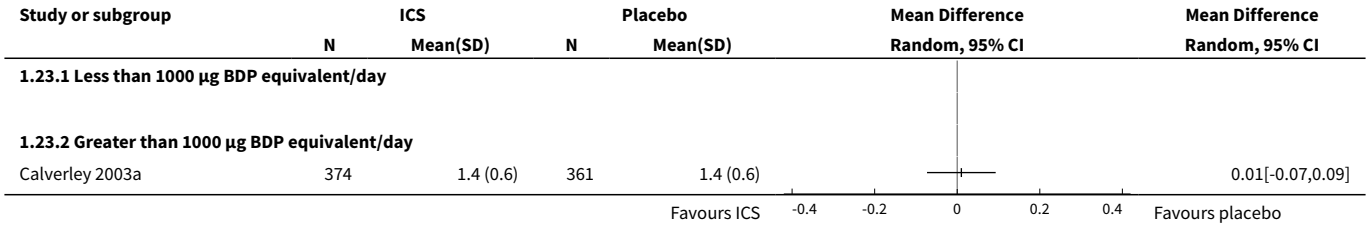


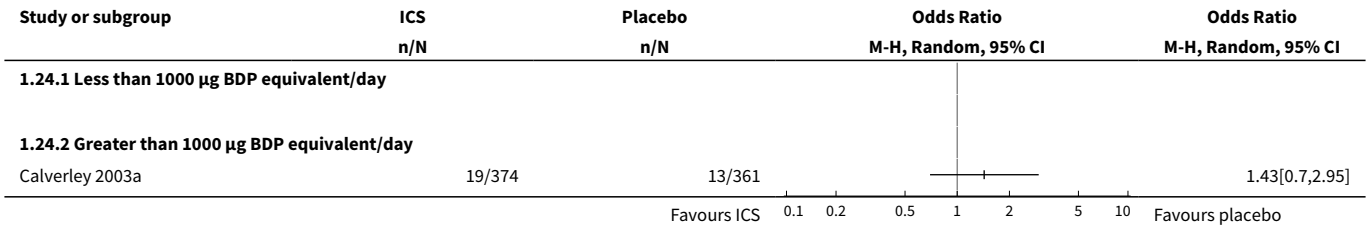
Analysis 1.22. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 22 Sputum production score.



Analysis 1.23. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 23 Sputum colour score.



Analysis 1.24. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 24 No. of patients with change from within to below normal for serum cortisol.



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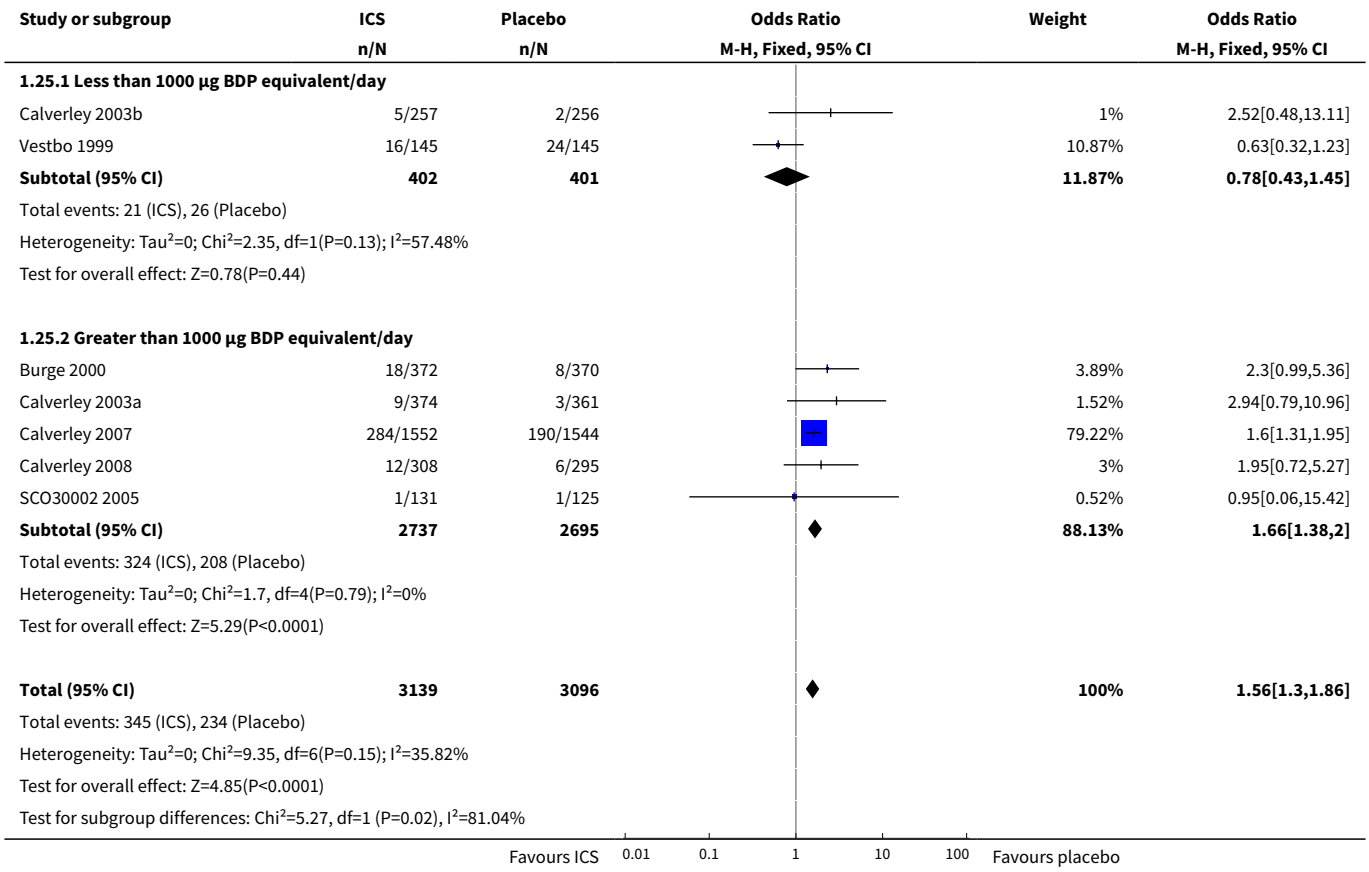
Analysis 1.25. Comparison 1 ICS versus placebo, parallel-group studies, greater than 6 months (all doses), Outcome 25 Pneumonia.



Comparison 2. ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in pre-bronchodilator FEV1 compared with baseline	7	2325	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.03, 0.06]
1.1 Less than 1000 µg BDP equivalent/day	2	985	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.01, 0.04]
1.2 Greater than 1000 µg BDP equivalent/day	6	1340	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.05, 0.10]
2 Change in post bronchodilator FEV1 compared to baseline (L)	4	1527	Mean Difference (IV, Random, 95% CI)	0.07 [0.01, 0.14]
2.1 Less than 1000 µg BDP equivalent/day	1	575	Mean Difference (IV, Random, 95% CI)	0.0 [-0.03, 0.03]
2.2 Greater than 1000 µg BDP equivalent/day	3	952	Mean Difference (IV, Random, 95% CI)	0.10 [0.06, 0.13]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Morning PEFR (L/min)	2	577	Mean Difference (IV, Random, 95% CI)	5.42 [0.59, 10.25]
3.1 Less than 1000 µg BDP equivalent/day	1	575	Mean Difference (IV, Random, 95% CI)	5.42 [0.59, 10.25]
3.2 Greater than 1000 µg BDP equivalent/day	1	2	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Post-bronchodilator FEV1 (change from baseline)	3	950	Litres (Fixed, 95% CI)	0.11 [0.07, 0.16]
4.1 Less than 1000 µg BDP equivalent/day	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Greater than 1000 µg BDP equivalent/day	3	950	Litres (Fixed, 95% CI)	0.11 [0.07, 0.16]
5 Change in pre-bronchodilator FEV1 compared with baseline	4	814	Litres (Fixed, 95% CI)	0.06 [0.02, 0.11]
5.1 Less than 1000 µg BDP equivalent/day	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Greater than 1000 µg BDP equivalent/day	4	814	Litres (Fixed, 95% CI)	0.06 [0.02, 0.11]
6 PEF (change scores)	2		Litres/min (Fixed, 95% CI)	Totals not selected
6.1 Less than 1000 µg BDP equivalent/day	1		Litres/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Greater than 1000 µg BDP equivalent/day	2		Litres/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
7 FVC (change from baseline)	1		Litres (Fixed, 95% CI)	Totals not selected
7.1 Less than 1000 µg BDP equivalent/day	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Greater than 1000 µg BDP equivalent/day	1		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Total number of deaths	5	1730	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.05, 1.28]
8.1 Less than 1000 µg BDP equivalent/day	1	422	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Greater than 1000 µg BDP equivalent/day	5	1308	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.05, 1.28]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 No. of patients with at least one exacerbation	5	1893	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.75, 1.08]
9.1 Less than 1000 µg BDP equivalent/day	3	839	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.71, 1.23]
9.2 Greater than 1000 µg BDP equivalent/day	3	1054	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.69, 1.12]
10 6-minute walk (change scores)	1		Metres (Fixed, 95% CI)	Totals not selected
10.1 Less than 1000 µg BDP equivalent/day	0		Metres (Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Greater than 1000 µg BDP equivalent/day	1		Metres (Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Change in 6-minute walk distance from baseline (m)	2	301	Mean Difference (IV, Random, 95% CI)	-4.36 [-50.42, 41.70]
11.1 Less than 1000 µg BDP equivalent/day	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Greater than 1000 µg BDP equivalent/day	2	301	Mean Difference (IV, Random, 95% CI)	-4.36 [-50.42, 41.70]
12 Change from baseline in dyspnoea on CRQ (units)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Change from baseline in emotion on CRQ (units)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 Change from baseline in fatigue on CRQ	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Change from baseline in mastery on CRQ (units)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16 Rescue beta-agonist use (puffs/day)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16.1 Less than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17 Throat irritation (no. of patients)	3	1572	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [1.09, 2.37]
17.1 Less than 1000 µg BDP equivalent/day	2	790	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.92, 2.79]
17.2 Greater than 1000 µg BDP equivalent/day	2	782	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.94, 2.79]
18 Oropharyngeal candidiasis (no. of patients)	5	2109	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.59 [3.58, 8.74]
18.1 Less than 1000 µg BDP equivalent/day	2	790	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.80 [2.20, 10.48]
18.2 Greater than 1000 µg BDP equivalent/day	4	1319	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.02 [3.50, 10.38]
19 Hoarseness or dysphonia (no. of patients)	4	1520	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.21 [2.17, 8.17]
19.1 Less than 1000 µg BDP equivalent/day	1	422	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.34 [1.55, 12.17]
19.2 Greater than 1000 µg BDP equivalent/day	4	1098	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.13 [1.74, 9.80]
20 Pneumonia (no. of patients)	1	846	Odds Ratio (M-H, Fixed, 95% CI)	1.91 [0.35, 10.47]
20.1 Less than 1000 µg BDP equivalent/day	1	422	Odds Ratio (M-H, Fixed, 95% CI)	1.92 [0.17, 21.29]
20.2 Greater than 1000 µg BDP equivalent/day	1	424	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [0.17, 21.09]

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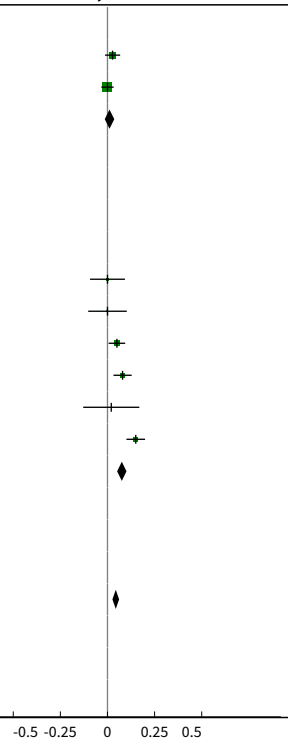
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 No. of patients with serum cortisol below normal range at any time	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
21.1 Less than 1000 µg BDP equivalent/day	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Greater than 1000 µg BDP equivalent/day	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 1 Change in pre-bronchodilator FEV1 compared with baseline.

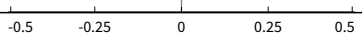
Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Less than 1000 µg BDP equivalent/day							
GSK 2005 (FLTA3025)	211	0 (0.2)	199	0 (0.2)		19.56%	0.03[-0.01,0.07]
Tashkin 2008	275	0 (0.2)	300	0 (0.2)		29.52%	0[-0.03,0.03]
Subtotal ***	**486**		**499**			**49.08%**	**0.01[-0.01,0.04]**
Heterogeneity: Tau^2=0; Chi^2=1.04, df=1(P=0.31); I^2=4.2%							
Test for overall effect: Z=0.83(P=0.41)							
2.1.2 Greater than 1000 µg BDP equivalent/day							
Bourbeau 1998	36	0 (0.2)	30	0 (0.2)		3.68%	0[-0.09,0.09]
GSK 2005 (FCO30002)	56	0 (0.3)	59	0 (0.3)		3.01%	0[-0.1,0.1]
GSK 2005 (FLTA3025)	210	0.1 (0.3)	199	0 (0.2)		16.36%	0.05[0.01,0.09]
Hanania 2003	183	0.1 (0.3)	185	0 (0.2)		13.52%	0.08[0.03,0.13]
Hattotuwa 2002	18	-0 (0.2)	15	-0.1 (0.3)		1.42%	0.02[-0.13,0.17]
Mahler 2002	168	0.1 (0.2)	181	-0 (0.2)		12.94%	0.15[0.1,0.2]
Subtotal ***	**671**		**669**			**50.92%**	**0.08[0.05,0.1]**
Heterogeneity: Tau^2=0; Chi^2=15.24, df=5(P=0.01); I^2=67.19%							
Test for overall effect: Z=5.98(P<0.0001)							
Total ***	**1157**		**1168**			**100%**	**0.04[0.03,0.06]**
Heterogeneity: Tau^2=0; Chi^2=29.22, df=7(P=0); I^2=76.04%							
Test for overall effect: Z=4.85(P<0.0001)							
Test for subgroup differences: Chi^2=12.93, df=1 (P=0), I^2=92.27%							



Favours placebo — Favours ICS

Analysis 2.2. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 2 Change in post bronchodilator FEV1 compared to baseline (L).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.2.1 Less than 1000 µg BDP equivalent/day							
Tashkin 2008	275	0 (0.2)	300	0 (0.2)		31.12%	0[-0.03,0.03]
Subtotal ***	**275**		**300**			**31.12%**	**0[-0.03,0.03]**



Favours placebo — Favours ICS

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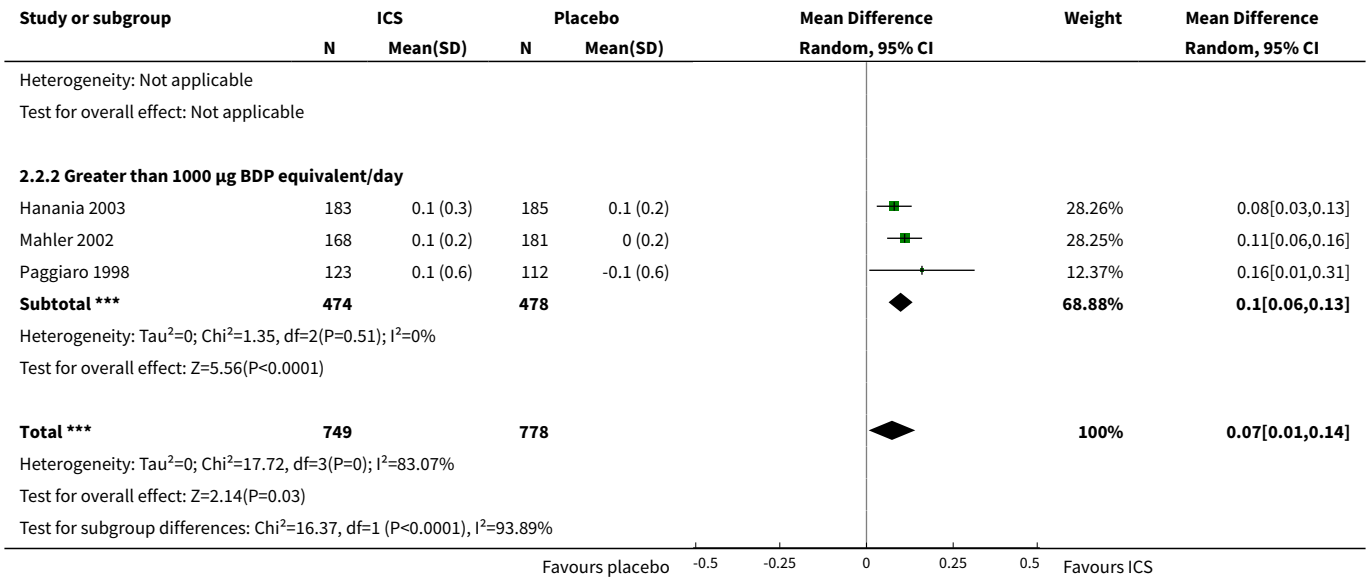
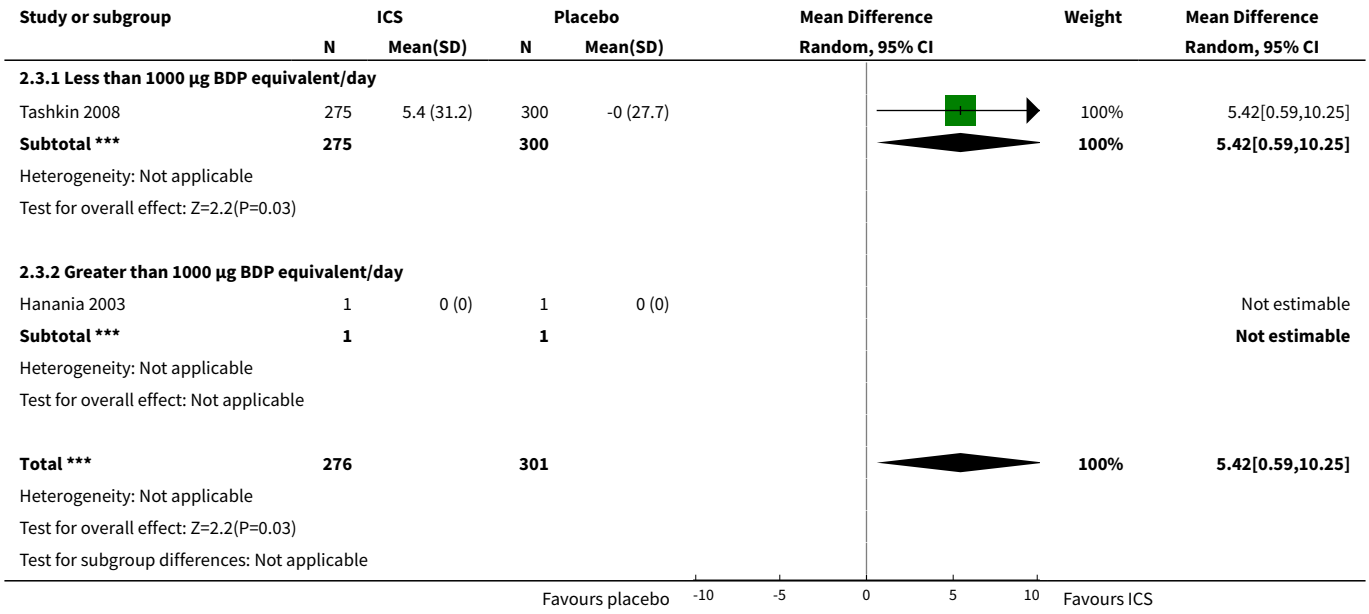
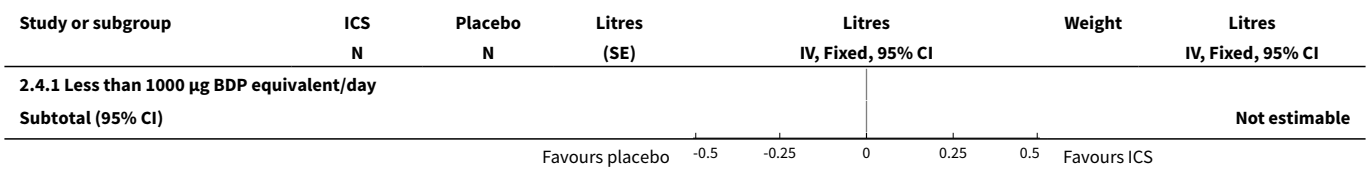


Analysis 2.3. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 3 Morning PEFR (L/min).



Analysis 2.4. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 4 Post-bronchodilator FEV1 (change from baseline).



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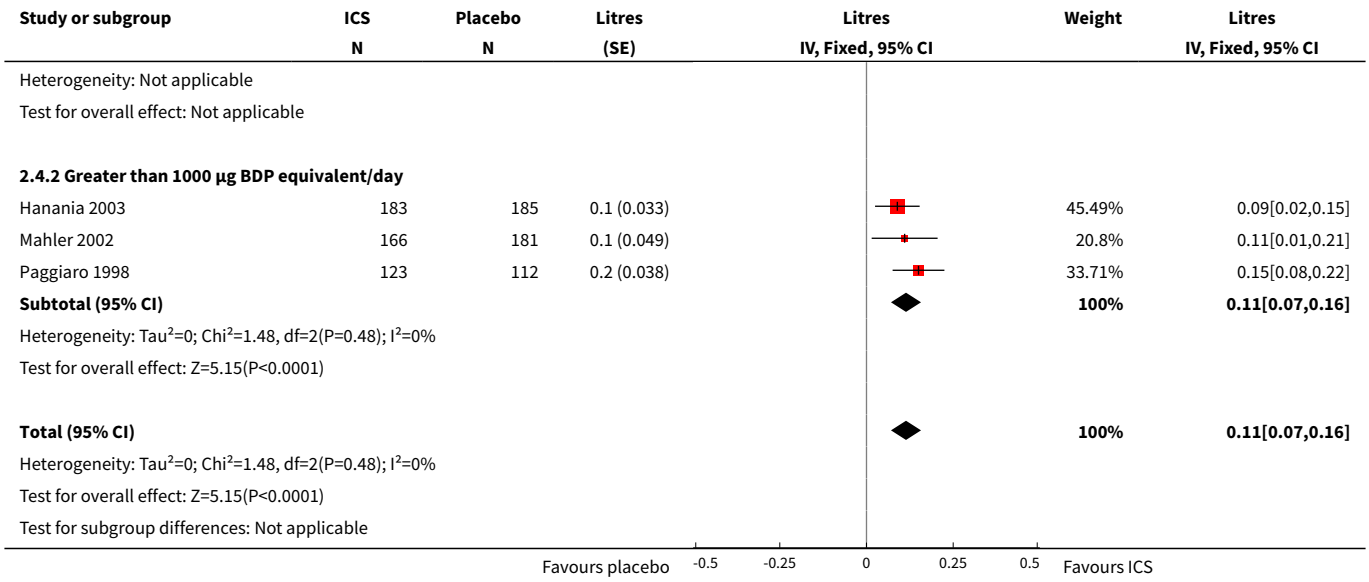
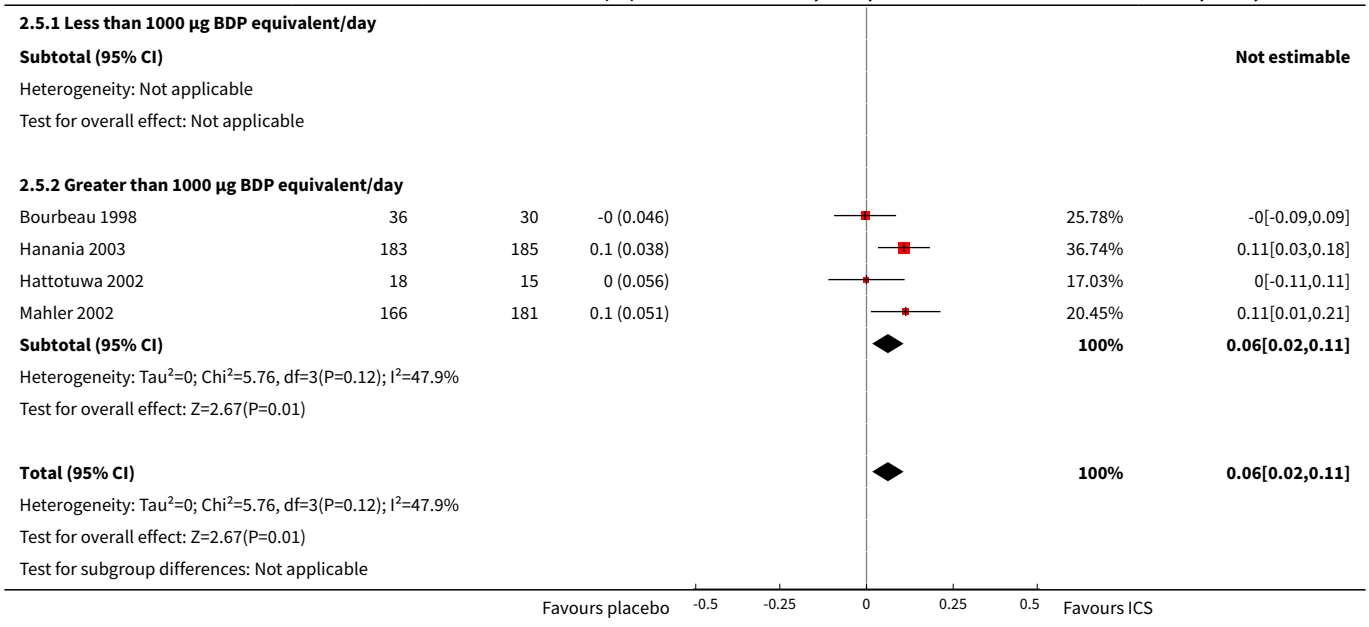


Analysis 2.5. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 5 Change in pre-bronchodilator FEV1 compared with baseline.



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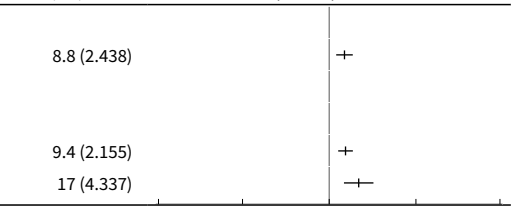
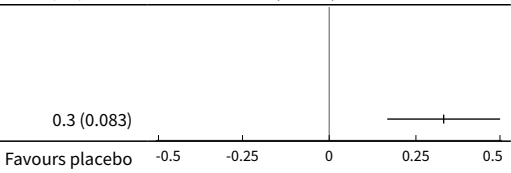
Analysis 2.6. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 6 PEF (change scores).

Study or subgroup	ICS N	Placebo N	Litres/min (SE)	Litres/min IV, Fixed, 95% CI	Litres/min IV, Fixed, 95% CI
2.6.1 Less than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	0	0	8.8 (2.438)		8.8[4.02,13.58]
2.6.2 Greater than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	0	0	9.4 (2.155)		9.4[5.18,13.62]
Paggiaro 1998	1	1	17 (4.337)		17[8.5,25.5]



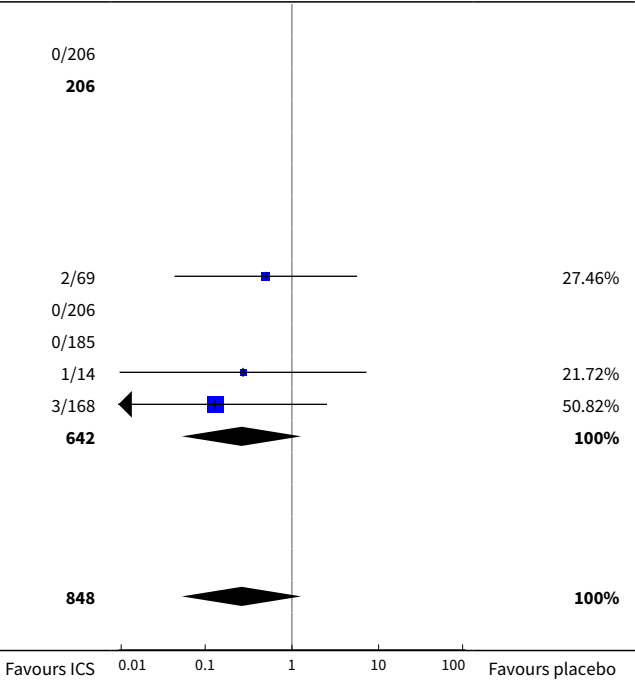
Analysis 2.7. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 7 FVC (change from baseline).

Study or subgroup	ICS N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
2.7.1 Less than 1000 µg BDP equivalent/day					
2.7.2 Greater than 1000 µg BDP equivalent/day					
Paggiaro 1998	1	1	0.3 (0.083)		0.33[0.17,0.49]



Analysis 2.8. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 8 Total number of deaths.

Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.8.1 Less than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	0/216	0/206			Not estimable
Subtotal (95% CI)	**216**	**206**			**Not estimable**
Total events: 0 (ICS), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.8.2 Greater than 1000 µg BDP equivalent/day					
GSK 2005 (FCO30002)	1/68	2/69		27.46%	0.5[0.04,5.65]
GSK 2005 (FLTA3025)	0/218	0/206			Not estimable
Hanania 2003	0/183	0/185			Not estimable
Hattotuwa 2002	0/16	1/14		21.72%	0.27[0.01,7.25]
Mahler 2002	0/181	3/168		50.82%	0.13[0.01,2.54]
Subtotal (95% CI)	**666**	**642**		**100%**	**0.26[0.05,1.28]**
Total events: 1 (ICS), 6 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.49, df=2(P=0.78); I^2=0%					
Test for overall effect: Z=1.65(P=0.1)					
Total (95% CI)	**882**	**848**		**100%**	**0.26[0.05,1.28]**
Total events: 1 (ICS), 6 (Placebo)					



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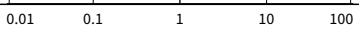
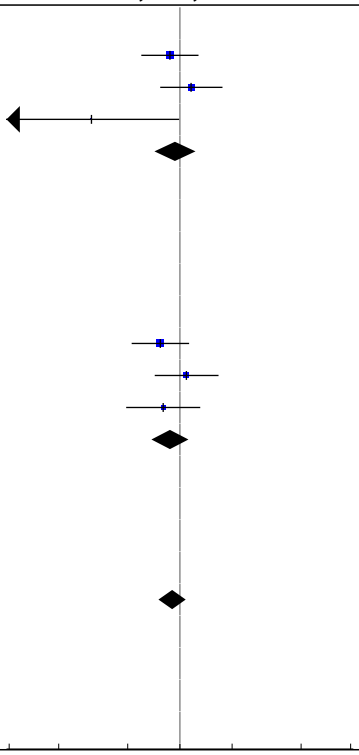
Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.49, df=2(P=0.78); I²=0%					
Test for overall effect: Z=1.65(P=0.1)					
Test for subgroup differences: Not applicable					



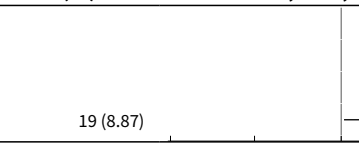
Analysis 2.9. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 9 No. of patients with at least one exacerbation.

Study or subgroup	ICS n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.9.1 Less than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	104/216	106/206		22.86%	0.88[0.6,1.28]
Hanania 2003	79/183	73/185		19.35%	1.16[0.77,1.76]
Laptseva 2002	13/25	19/24		2.45%	0.31[0.1,0.99]
Subtotal (95% CI)	**424**	**415**		**44.66%**	**0.94[0.71,1.23]**
Total events: 196 (ICS), 198 (Placebo)					
Heterogeneity: Tau²=0; Chi²=4.66, df=2(P=0.1); I²=57.12%					
Test for overall effect: Z=0.47(P=0.64)					
2.9.2 Greater than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	98/218	106/206		22.93%	0.77[0.53,1.13]
Mahler 2002	77/168	79/181		18.69%	1.09[0.72,1.67]
Paggiaro 1998	45/142	51/139		13.72%	0.8[0.49,1.31]
Subtotal (95% CI)	**528**	**526**		**55.34%**	**0.88[0.69,1.12]**
Total events: 220 (ICS), 236 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.61, df=2(P=0.45); I²=0%					
Test for overall effect: Z=1.06(P=0.29)					
Total (95% CI)	**952**	**941**		**100%**	**0.9[0.75,1.08]**
Total events: 416 (ICS), 434 (Placebo)					
Heterogeneity: Tau²=0; Chi²=6.4, df=5(P=0.27); I²=21.87%					
Test for overall effect: Z=1.11(P=0.27)					
Test for subgroup differences: Chi²=0.13, df=1 (P=0.72), I²=0%					



Analysis 2.10. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 10 6-minute walk (change scores).

Study or subgroup	ICS N	Placebo N	Metres (SE)	Metres IV, Fixed, 95% CI	Metres IV, Fixed, 95% CI
2.10.1 Less than 1000 µg BDP equivalent/day					
2.10.2 Greater than 1000 µg BDP equivalent/day					
Paggiaro 1998	1	1	19 (8.87)		19[1.62,36.38]



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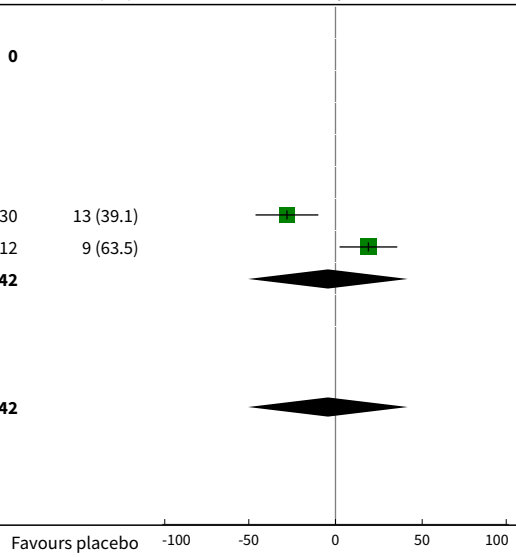
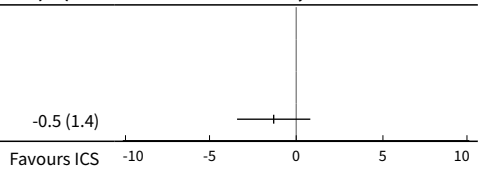
Analysis 2.11. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 11 Change in 6-minute walk distance from baseline (m).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.11.1 Less than 1000 µg BDP equivalent/day							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.11.2 Greater than 1000 µg BDP equivalent/day							
Bourbeau 1998	36	-15 (35.2)	30	13 (39.1)		49.7%	-28[-46.12,-9.88]
Paggiaro 1998	123	28 (66.5)	112	9 (63.5)		50.3%	19[2.37,35.63]
Subtotal ***	**159**		**142**			**100%**	**-4.36[-50.42,41.7]**
Heterogeneity: Tau^2=1025.79; Chi^2=14.03, df=1(P=0); I^2=92.87%							
Test for overall effect: Z=0.19(P=0.85)							
Total ***	**159**		**142**			**100%**	**-4.36[-50.42,41.7]**
Heterogeneity: Tau^2=1025.79; Chi^2=14.03, df=1(P=0); I^2=92.87%							
Test for overall effect: Z=0.19(P=0.85)							
Test for subgroup differences: Not applicable							



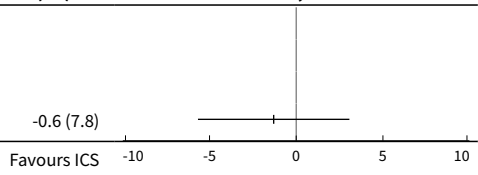
Analysis 2.12. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 12 Change from baseline in dyspnoea on CRQ (units).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.12.1 Less than 1000 µg BDP equivalent/day						
2.12.2 Greater than 1000 µg BDP equivalent/day						
Bourbeau 1998	36	-1.8 (6.3)	30	-0.5 (1.4)		-1.3[-3.41,0.81]



Analysis 2.13. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 13 Change from baseline in emotion on CRQ (units).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.13.1 Less than 1000 µg BDP equivalent/day						
2.13.2 Greater than 1000 µg BDP equivalent/day						
Bourbeau 1998	36	-1.9 (10.3)	30	-0.6 (7.8)		-1.3[-5.67,3.07]



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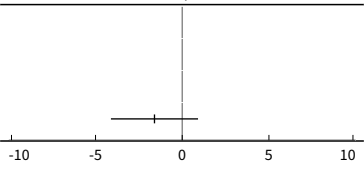
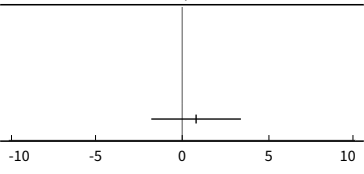
Analysis 2.14. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 14 Change from baseline in fatigue on CRQ.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.14.1 Less than 1000 µg BDP equivalent/day						
2.14.2 Greater than 1000 µg BDP equivalent/day						
Bourbeau 1998	36	-3 (5.7)	30	-1.4 (4.8)		-1.6[-4.11,0.91]



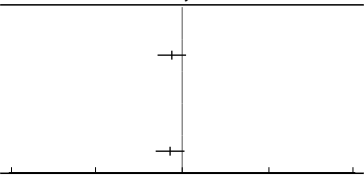
Analysis 2.15. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 15 Change from baseline in mastery on CRQ (units).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.15.1 Less than 1000 µg BDP equivalent/day						
2.15.2 Greater than 1000 µg BDP equivalent/day						
Bourbeau 1998	36	-0.5 (5.8)	30	-1.3 (4.9)		0.8[-1.78,3.38]



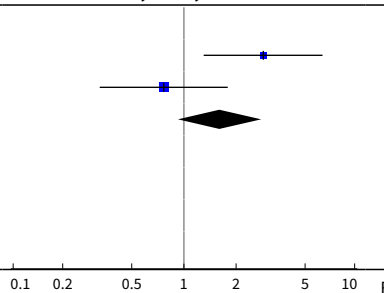
Analysis 2.16. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 16 Rescue beta-agonist use (puffs/day).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.16.1 Less than 1000 µg BDP equivalent/day						
GSK 2005 (FLTA3025)	214	5.6 (4.4)	205	6.2 (4.1)		-0.6[-1.42,0.22]
2.16.2 Greater than 1000 µg BDP equivalent/day						
GSK 2005 (FLTA3025)	215	5.5 (4.5)	205	6.2 (4.1)		-0.7[-1.53,0.13]



Analysis 2.17. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 17 Throat irritation (no. of patients).

Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.17.1 Less than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	25/216	9/206		19.76%	2.87[1.3,6.3]
Hanania 2003	10/183	13/185		29.64%	0.76[0.33,1.79]
Subtotal (95% CI)	**399**	**391**		**49.4%**	**1.6[0.92,2.79]**
Total events: 35 (ICS), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.99, df=1(P=0.03); I^2=79.98%					
Test for overall effect: Z=1.68(P=0.09)					



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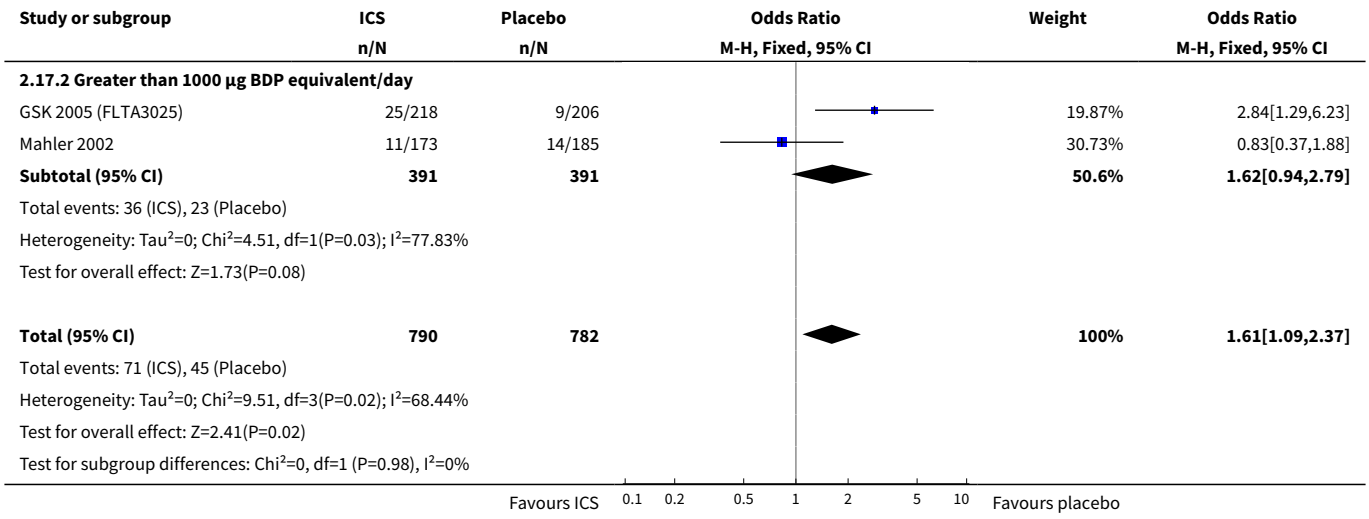
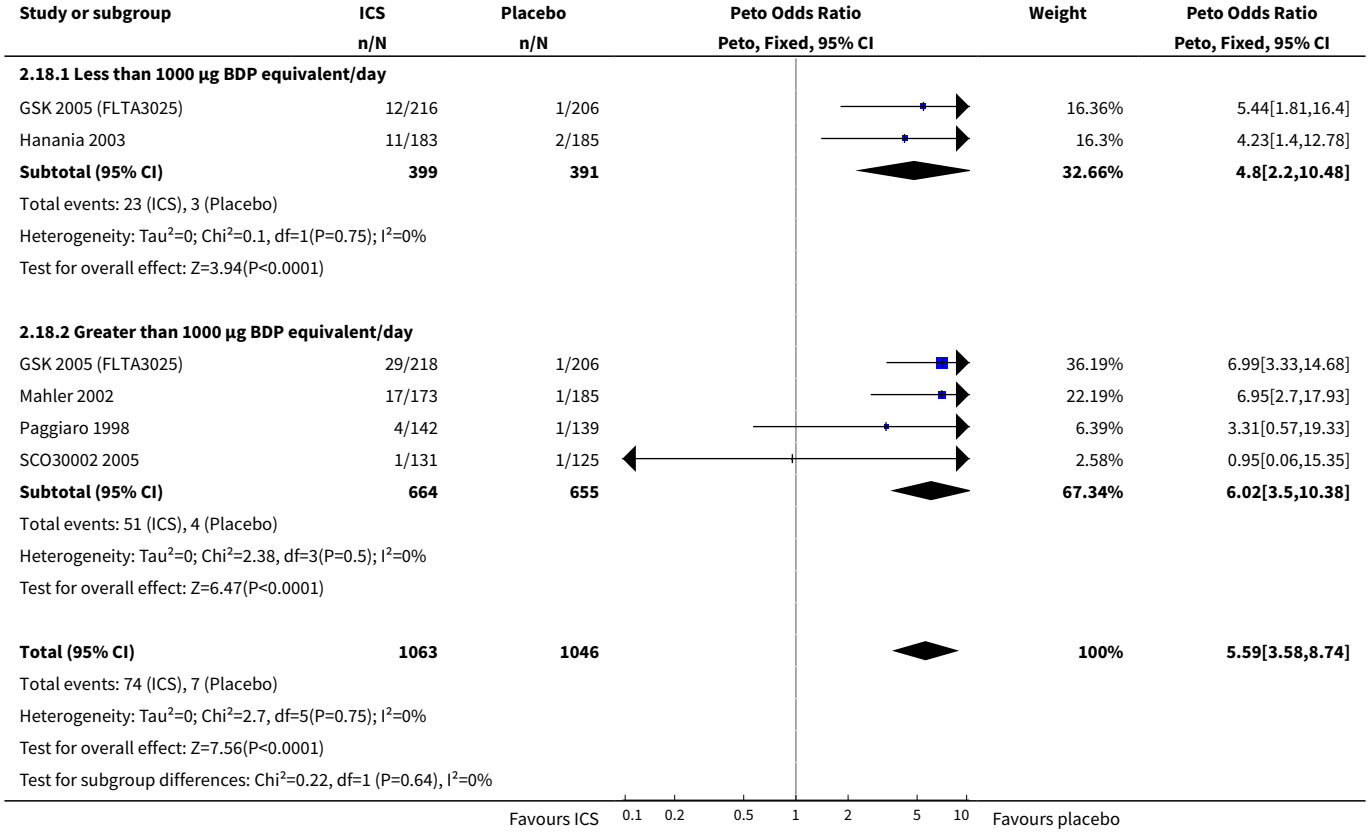


Analysis 2.18. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 18 Oropharyngeal candidiasis (no. of patients).



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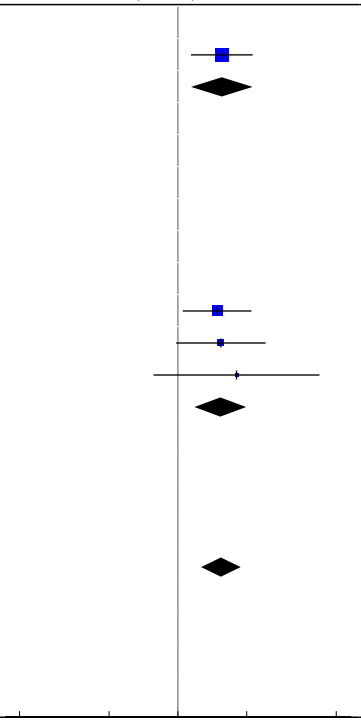
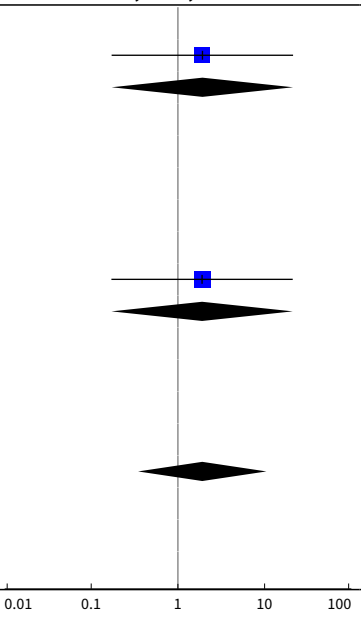
Analysis 2.19. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 19 Hoarseness or dysphonia (no. of patients).

Study or subgroup	ICS n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.19.1 Less than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	13/216	2/206		41.39%	4.34[1.55,12.17]
Subtotal (95% CI)	**216**	**206**		**41.39%**	**4.34[1.55,12.17]**
Total events: 13 (ICS), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.8(P=0.01)					
2.19.2 Greater than 1000 µg BDP equivalent/day					
GSK 2005 (FCO30002)	0/68	0/69			Not estimable
GSK 2005 (FLTA3025)	10/218	2/206		33.36%	3.71[1.18,11.69]
Paggiaro 1998	6/142	1/139		19.56%	4.21[0.94,18.84]
SCO30002 2005	2/131	0/125		5.69%	7.11[0.44,114.42]
Subtotal (95% CI)	**559**	**539**		**58.61%**	**4.13[1.74,9.8]**
Total events: 18 (ICS), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=2(P=0.91); I^2=0%					
Test for overall effect: Z=3.21(P=0)					
Total (95% CI)	**775**	**745**		**100%**	**4.21[2.17,8.17]**
Total events: 31 (ICS), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=3(P=0.98); I^2=0%					
Test for overall effect: Z=4.26(P<0.0001)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.94), I^2=0%					



Analysis 2.20. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 20 Pneumonia (no. of patients).

Study or subgroup	ICS n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.20.1 Less than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	2/216	1/206		49.89%	1.92[0.17,21.29]
Subtotal (95% CI)	**216**	**206**		**49.89%**	**1.92[0.17,21.29]**
Total events: 2 (ICS), 1 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.6)					
2.20.2 Greater than 1000 µg BDP equivalent/day					
GSK 2005 (FLTA3025)	2/218	1/206		50.11%	1.9[0.17,21.09]
Subtotal (95% CI)	**218**	**206**		**50.11%**	**1.9[0.17,21.09]**
Total events: 2 (ICS), 1 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					
Total (95% CI)	**434**	**412**		**100%**	**1.91[0.35,10.47]**
Total events: 4 (ICS), 2 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.74(P=0.46)					



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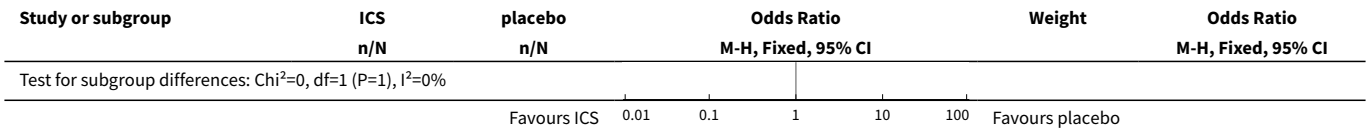
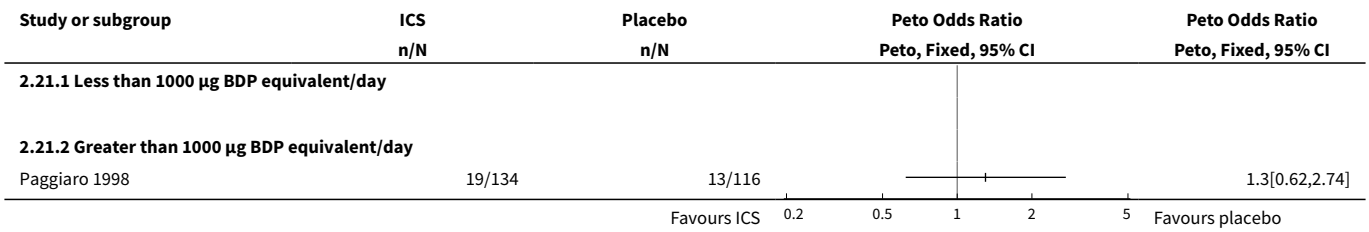


Analysis 2.21. Comparison 2 ICS versus placebo, parallel-group studies, greater than 2 months to 6 months (all doses), Outcome 21 No. of patients with serum cortisol below normal range at any time.



Comparison 3. ICS versus placebo, parallel-group studies, 2 months or less (all doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 compared to baseline (% increase)	2	57	Mean Difference (IV, Random, 95% CI)	3.84 [-4.82, 12.50]
1.1 Less than 1000 µg BDP equivalent/day	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Greater than 1000 µg BDP equivalent/day	2	57	Mean Difference (IV, Random, 95% CI)	3.84 [-4.82, 12.50]
2 Change in FVC compared to baseline (% increase)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Change in MMEFR compared to baseline (% increase)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Morning PEFR (L/min)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Evening PEFR (L/min)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Change in PEFR compared to baseline (% increase)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 No. of patients with at least one exacerbation	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Less than 1000 µg BDP equivalent/day	0		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Greater than 1000 µg BDP equivalent/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Rescue beta-agonist use (puffs/day)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Oropharyngeal candidiasis (no. of patients)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 Less than 1000 µg BDP equivalent/day	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Greater than 1000 µg BDP equivalent/day	0		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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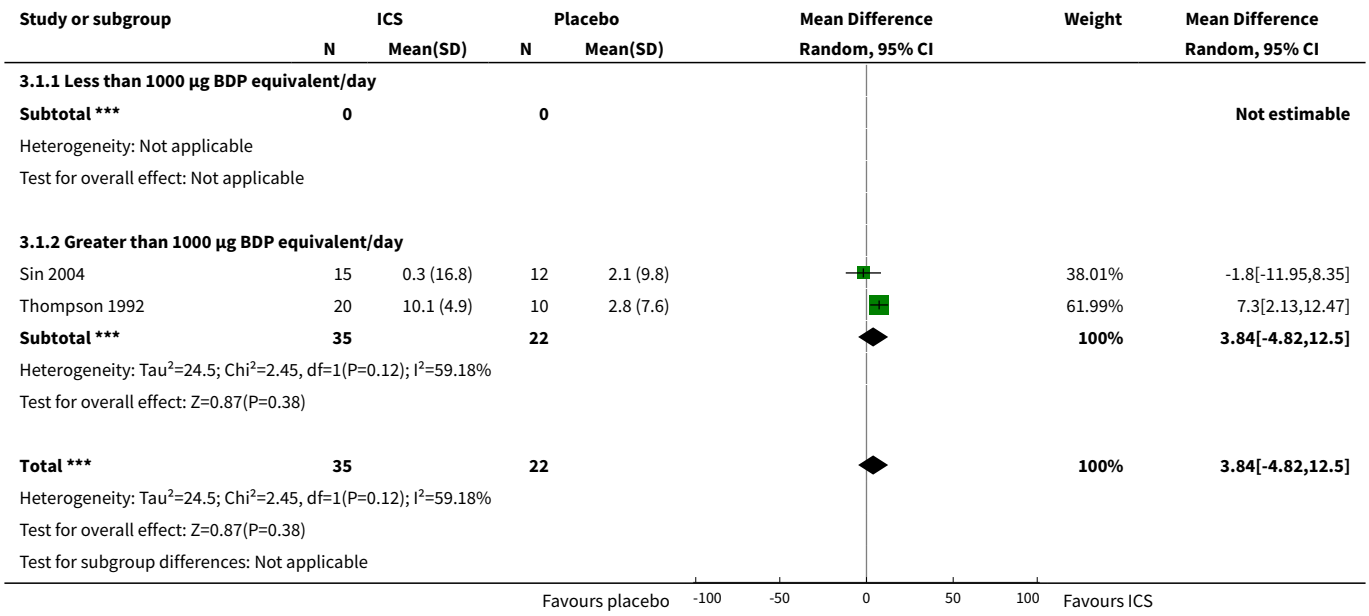
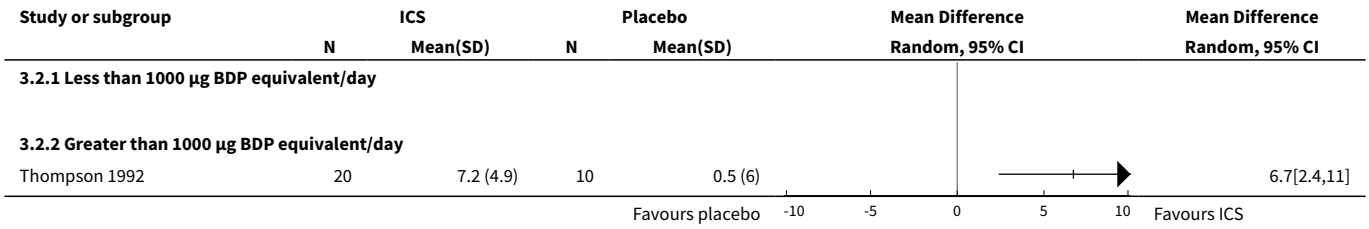
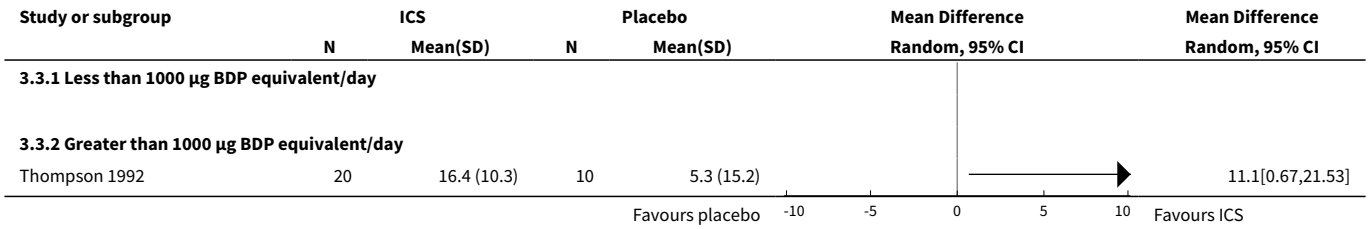
Analysis 3.1. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 1 Change in FEV1 compared to baseline (% increase).



Analysis 3.2. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 2 Change in FVC compared to baseline (% increase).



Analysis 3.3. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 3 Change in MMEFR compared to baseline (% increase).



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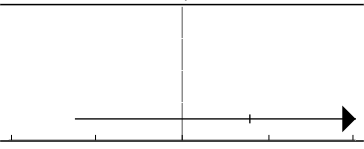
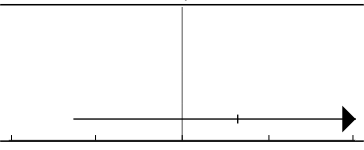
Analysis 3.4. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 4 Morning PEFR (L/min).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.4.1 Less than 1000 µg BDP equivalent/day						
3.4.2 Greater than 1000 µg BDP equivalent/day						
Llewellyn-Jones 1996	8	194 (123.6)	8	155 (76.9)		39[-61.88,139.88]



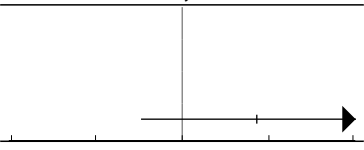
Analysis 3.5. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 5 Evening PEFR (L/min).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.5.1 Less than 1000 µg BDP equivalent/day						
3.5.2 Greater than 1000 µg BDP equivalent/day						
Llewellyn-Jones 1996	8	201 (121.3)	8	169 (63.1)		32[-62.76,126.76]



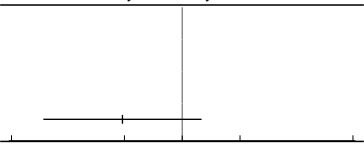
Analysis 3.6. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 6 Change in PEFR compared to baseline (% increase).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.6.1 Less than 1000 µg BDP equivalent/day						
3.6.2 Greater than 1000 µg BDP equivalent/day						
Thompson 1992	20	9.3 (9.8)	10	5 (8.2)		4.3[-2.37,10.97]



Analysis 3.7. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 7 No. of patients with at least one exacerbation.

Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
3.7.1 Less than 1000 µg BDP equivalent/day				
3.7.2 Greater than 1000 µg BDP equivalent/day				
Llewellyn-Jones 1996	0/8	3/8		0.09[0,2.16]



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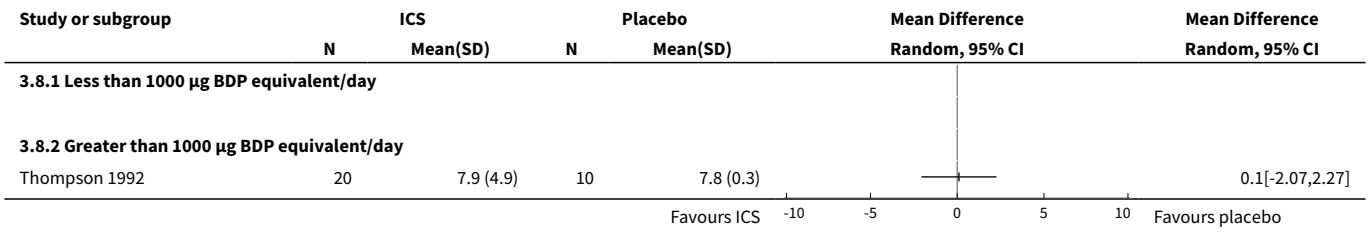
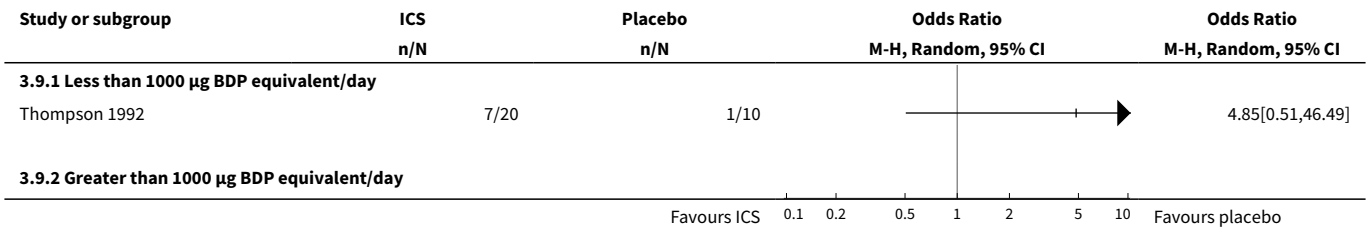
Analysis 3.8. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 8 Rescue beta-agonist use (puffs/day).



Analysis 3.9. Comparison 3 ICS versus placebo, parallel-group studies, 2 months or less (all doses), Outcome 9 Oropharyngeal candidiasis (no. of patients).



Comparison 4. ICS versus placebo, cross-over studies, 2 months or less (all doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2	396	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.05, 0.32]
1.1 Less than 1000 µg BDP equivalent/day	1	336	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.16, 0.74]
1.2 Greater than 1000 µg BDP equivalent/day	1	60	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.10, 0.30]
2 Daily PEFR (L/min)	2	86	Mean Difference (IV, Fixed, 95% CI)	18.78 [-20.17, 57.72]
2.1 Less than 1000 µg BDP equivalent/day	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Greater than 1000 µg BDP equivalent/day	2	86	Mean Difference (IV, Fixed, 95% CI)	18.78 [-20.17, 57.72]
3 FEV1 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

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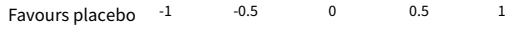
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Rescue beta-agonist use (puffs/day)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Less than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Greater than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in post-bronchodilator FEV1	1		L (Fixed, 95% CI)	Totals not selected

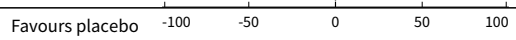
Analysis 4.1. Comparison 4 ICS versus placebo, cross-over studies, 2 months or less (all doses), Outcome 1 FEV1 (L).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.1.1 Less than 1000 µg BDP equivalent/day							
Weiner 1999	168	1.6 (2.2)	168	1.3 (2.1)		17.16%	0.29[-0.16,0.74]
Subtotal ***	**168**		**168**			**17.16%**	**0.29[-0.16,0.74]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.26(P=0.21)							
4.1.2 Greater than 1000 µg BDP equivalent/day							
Nishimura 1999	30	1.3 (0.4)	30	1.2 (0.4)		82.84%	0.1[-0.1,0.3]
Subtotal ***	**30**		**30**			**82.84%**	**0.1[-0.1,0.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.96(P=0.34)							
Total ***	**198**		**198**			**100%**	**0.13[-0.05,0.32]**
Heterogeneity: Tau^2=0; Chi^2=0.57, df=1(P=0.45); I^2=0%							
Test for overall effect: Z=1.39(P=0.16)							
Test for subgroup differences: Chi^2=0.57, df=1 (P=0.45), I^2=0%							



Analysis 4.2. Comparison 4 ICS versus placebo, cross-over studies, 2 months or less (all doses), Outcome 2 Daily PEFR (L/min).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.2.1 Less than 1000 µg BDP equivalent/day							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



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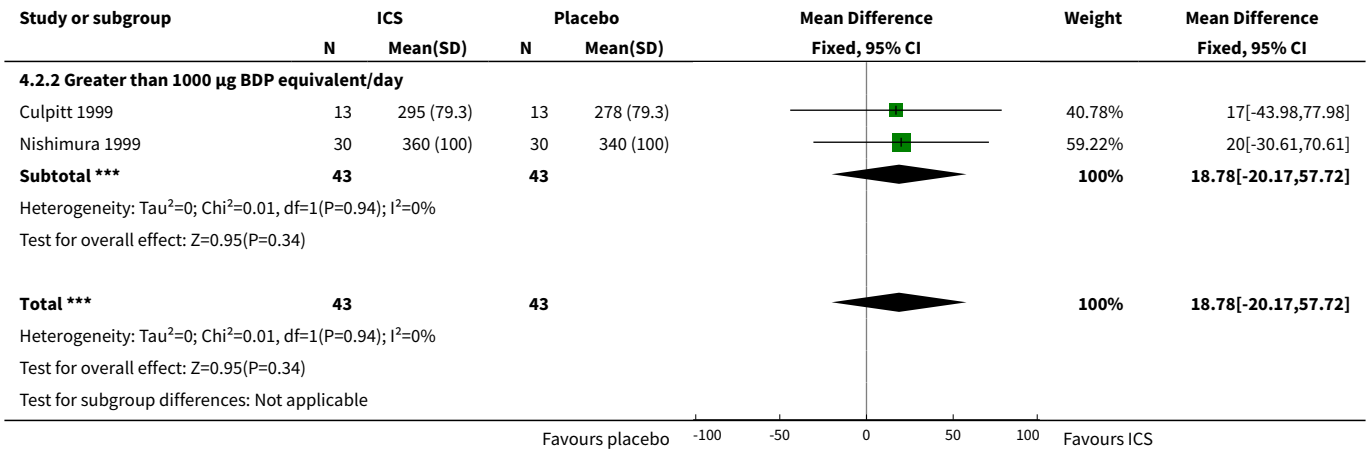
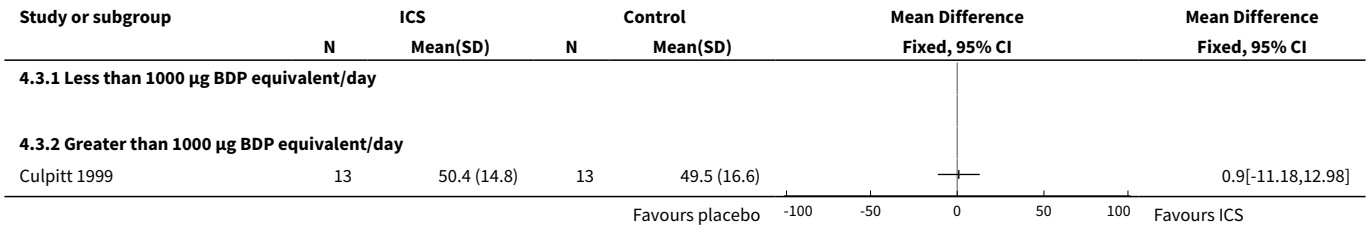
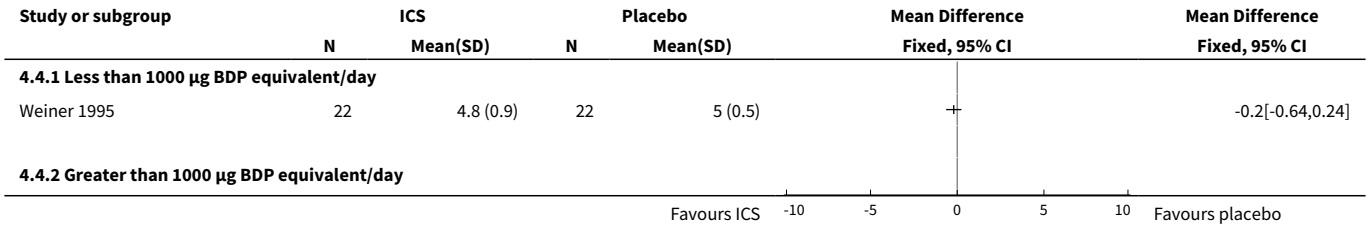


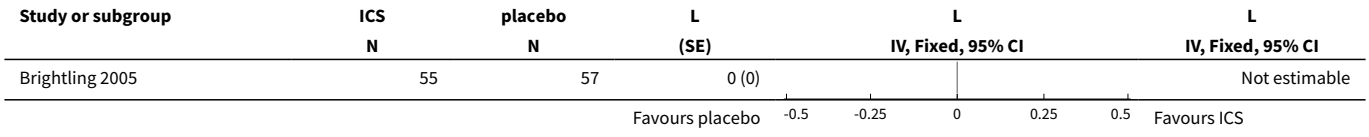
Analysis 4.3. Comparison 4 ICS versus placebo, cross-over studies, 2 months or less (all doses), Outcome 3 FEV1 % predicted.



Analysis 4.4. Comparison 4 ICS versus placebo, cross-over studies, 2 months or less (all doses), Outcome 4 Rescue beta-agonist use (puffs/day).



Analysis 4.5. Comparison 4 ICS versus placebo, cross-over studies, 2 months or less (all doses), Outcome 5 Change in post-bronchodilator FEV1.



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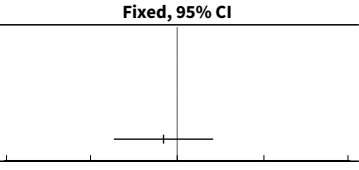
Comparison 5. ICS versus placebo, studies of COPD with BHR, greater than 2 months to 6 months (all doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Salbutamol rescue doses (per month)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Ipratropium rescue doses (per month)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Serum cortisol at 6 months (nM/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

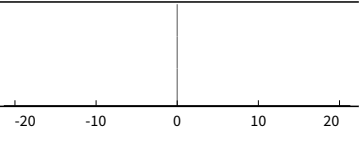
Analysis 5.1. Comparison 5 ICS versus placebo, studies of COPD with BHR, greater than 2 months to 6 months (all doses), Outcome 1 Salbutamol rescue doses (per month).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.1.1 Less than 1000 µg BDP equivalent/day						
5.1.2 Greater than 1000 µg BDP equivalent/day						
Verhoeven 2002	10	32.5 (27)	13	40.4 (42.7)		-7.9[-36.52,20.72]



Analysis 5.2. Comparison 5 ICS versus placebo, studies of COPD with BHR, greater than 2 months to 6 months (all doses), Outcome 2 Ipratropium rescue doses (per month).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.2.1 Less than 1000 µg BDP equivalent/day						
5.2.2 Greater than 1000 µg BDP equivalent/day						



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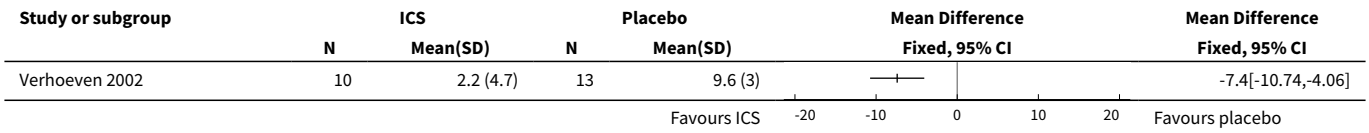
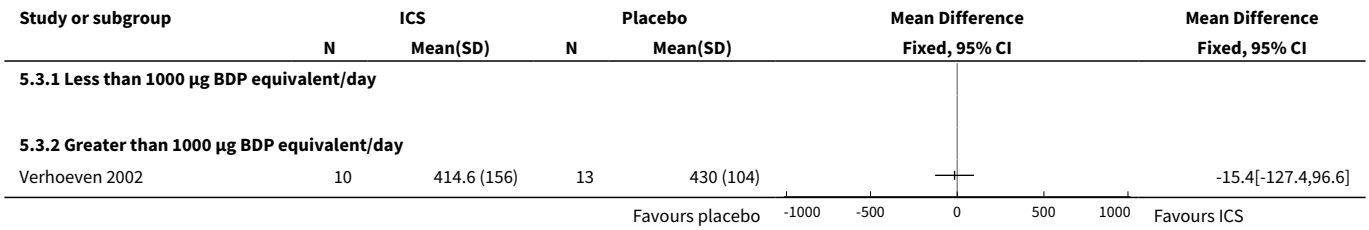


Analysis 5.3. Comparison 5 ICS versus placebo, studies of COPD with BHR, greater than 2 months to 6 months (all doses), Outcome 3 Serum cortisol at 6 months (nM/L).



Comparison 6. ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in pre-bronchodilator FEV1 compared to baseline (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in pre-bronchodilator VC compared to baseline (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in FEV1 before terbutaline as % baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in FEV1 after terbutaline as % baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in log10 PC20 histamine	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change in log10 citric acid threshold	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Change in morning peak expiratory flow rate (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Change in evening peak expiratory flow rate (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Change in dyspnoea score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Change in cough score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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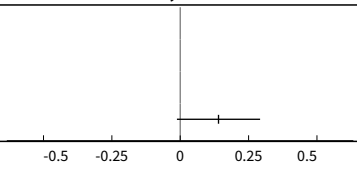
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Change in sputum score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Change in rescue bronchodilator usage (puffs/day)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Less than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Greater than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Change in post-bronchodilator FEV1 (mL/yr)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Less than 1000 µg BDP equivalent/day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Greater than 1000 µg BDP equivalent/day	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 1 Change in pre-bronchodilator FEV1 compared to baseline (L).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.1.1 Less than 1000 µg BDP equivalent/day						
6.1.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	10	0 (0.1)	11	-0.1 (0.2)		0.14[-0.01,0.29]



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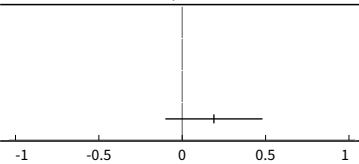
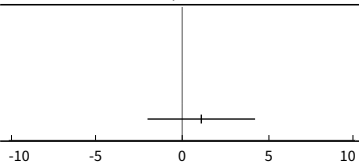
Analysis 6.2. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 2 Change in pre-bronchodilator VC compared to baseline (L).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.2.1 Less than 1000 µg BDP equivalent/day						
6.2.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	10	0.3 (0.2)	11	0.1 (0.4)		0.19[-0.1,0.48]



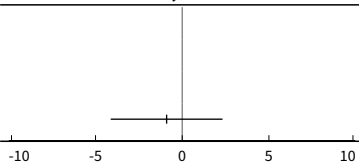
Analysis 6.3. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 3 Change in FEV1 before terbutaline as % baseline.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.3.1 Less than 1000 µg BDP equivalent/day						
6.3.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	10	7.2 (4.4)	11	6.1 (2.5)		1.1[-2,4.2]



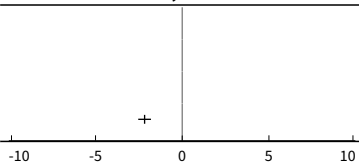
Analysis 6.4. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 4 Change in FEV1 after terbutaline as % baseline.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.4.1 Less than 1000 µg BDP equivalent/day						
6.4.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	10	6.5 (5)	11	7.4 (1.5)		-0.9[-4.12,2.32]



Analysis 6.5. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 5 Change in log10 PC20 histamine.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.5.1 Less than 1000 µg BDP equivalent/day						
6.5.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	10	-2.1 (0.4)	11	0.1 (0.5)		-2.17[-2.54,-1.8]



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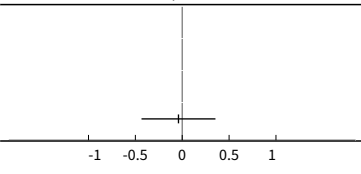
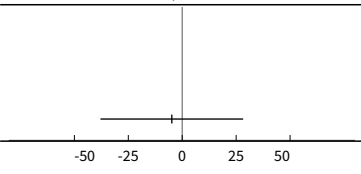
Analysis 6.6. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 6 Change in log10 citric acid threshold.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.6.1 Less than 1000 µg BDP equivalent/day						
6.6.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	10	-0.2 (0.5)	11	-0.1 (0.5)		-0.04[-0.43,0.35]



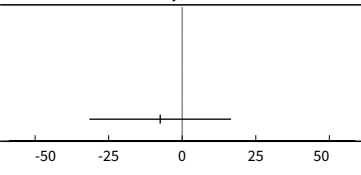
Analysis 6.7. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 7 Change in morning peak expiratory flow rate (L/min).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.7.1 Less than 1000 µg BDP equivalent/day						
6.7.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	12	-2.8 (47)	11	2 (33.3)		-4.83[-37.91,28.25]



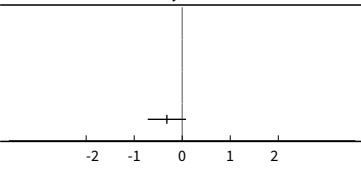
Analysis 6.8. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 8 Change in evening peak expiratory flow rate (L/min).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.8.1 Less than 1000 µg BDP equivalent/day						
6.8.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	12	-13.2 (36.2)	11	-5.7 (21.4)		-7.48[-31.55,16.59]



Analysis 6.9. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 9 Change in dyspnoea score.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.9.1 Less than 1000 µg BDP equivalent/day						
6.9.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	12	-0.2 (0.3)	11	0.1 (0.6)		-0.32[-0.72,0.08]



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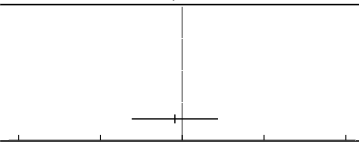
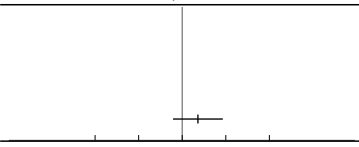
Analysis 6.10. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 10 Change in cough score.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.10.1 Less than 1000 µg BDP equivalent/day						
6.10.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	12	-0.2 (0.5)	11	-0.1 (0.8)		-0.09[-0.62,0.44]



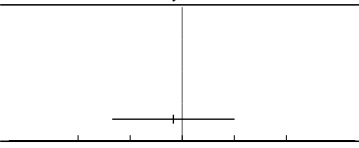
Analysis 6.11. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 11 Change in sputum score.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.11.1 Less than 1000 µg BDP equivalent/day						
6.11.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	12	0 (0.2)	11	-0.3 (1)		0.36[-0.21,0.93]



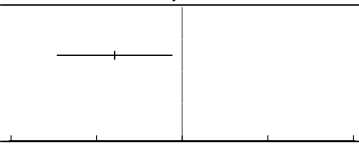
Analysis 6.12. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 12 Change in rescue bronchodilator usage (puffs/day).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.12.1 Less than 1000 µg BDP equivalent/day						
6.12.2 Greater than 1000 µg BDP equivalent/day						
Auffarth 1991	12	0.5 (1.8)	11	0.7 (1.1)		-0.17[-1.34,1]



Analysis 6.13. Comparison 6 ICS versus placebo, studies of COPD with BHR, greater than 6 months (all doses), Outcome 13 Change in post-bronchodilator FEV1 (mL/yr).

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.13.1 Less than 1000 µg BDP equivalent/day						
van Grunsven 2003	24	-93 (147)	24	-14 (83.3)		-79[-146.58,-11.42]
6.13.2 Greater than 1000 µg BDP equivalent/day						



ADDITIONAL TABLES

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Table 1. Search history detail

Year	Abstracts retrieved
Up to and including 1999	1340
2000	464
2001	131
2002	34
2003	72
2004	116
2005	48
2006	40
2007	62
2008	100
2009-10	60
2011	77

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*the Cochrane Library*)	Quarterly
PSYCINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

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Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomized or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

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11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

F E E D B A C K

Feedback regarding TORCH study, 23 June 2016

Summary

We read your review with great interest, and thank the authors for clarifying and updating the evidence for inhaled corticosteroids (ICS) in COPD patients. Our group have some concerns regarding the evaluation of the TOwards A Revolution in COPD Health (TORCH) trial, which we feel may benefit from some clarification by the authorship team. We feel the TORCH trial may have a higher risk of bias than its attributed overall 'low' rating which may impact upon the review findings considering its large size. This is due to the following observations:

1. The TORCH protocol indicates that an intention-to-treat (ITT) analysis was to be conducted (3), however, following randomization 72 (1.2%) participants were excluded from five independent study sites because of unblinding caused by: fraudulent data, falsified signatures, failure to follow GCP and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical use for Human Use guidelines, and compromised patient safety (1). 38.3% participant withdrawal occurred prior to study completion. The TORCH authors state that “adverse events included death during the study period but may not have included deaths occurring after patients withdrew from the study” (2) which appears to contradict the protocol that indicated outcome data would be collected for the duration of the study for all enrolled and randomized participants (3). It is unclear whether mortality outcomes were collected for the duration of the study in participants who withdrew early. This analysis may not therefore constitute an ITT, and may have underestimated the incidence of mortality in all treatment arms.
2. The TORCH study authors did not provide clear criteria related to symptoms for the definition of an acute exacerbation which may make it difficult to conclude significant benefit of inhaled corticosteroids on moderate to severe exacerbations. Their analysis of exacerbations per patient per year may be affected by a small portion of patients who experience a large number of exacerbations per year when reported as a mean. And it is unclear whether exacerbations were recorded once participants withdrew or were excluded from the trial, contrary to their pre-specified protocol (2).
3. As study participants were screened for adverse effects and changes in FEV1 by physicians approximately every 12 and 24 weeks, we feel there is potential for both study participants and personnel to have become unblinded to treatments posing risks of performance and/or detection bias. The decrease in number of exacerbations in participants receiving fluticasone when compared to placebo may therefore not necessarily yield the same results once this is taken into account.
4. In their primary analysis of St. George's Respiratory Questionnaire (SGRQ) data, the TORCH study authors only included data from “linguistically valid translations” (2). 36% of participants were not included as part of the author's primary analyses, with 19% initially reported as having not completed a validated questionnaire. A further 21% were censored despite having competed a linguistically valid SGRQ. The precise reasons for these observations are unclear, however the significant attrition, potentially caused by compromised randomization, may affect conclusions about the efficacy of fluticasone on patient-reported quality of life. We believe your statement that fluticasone confers a mean “benefit” of -2.0 units over 3 years when compared to placebo as derived from the TORCH trial may be better expressed in the context of the margin being below the threshold difference of four points for clinical significance, and the data are likely incomplete (4).

Our independent analysis of the risk of bias for the TORCH trial is as follows: Selection bias (low), performance bias (unclear), detection bias (unclear), attrition bias (high), reporting bias (low).

References

1. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. NEJM. 2007; 356: 775-89. DOI: 10.1056/NEJMoa063070 Supplementary Appendix 2,Online Figure 1, p11
2. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. NEJM. 2007; 356: 775-89. DOI: 10.1056/NEJMoa063070
3. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. NEJM. 2007; 356: 775-89. DOI: 10.1056/NEJMoa063070 Supplementary Appendix 1
4. Aaron SD, Fergusson D, Marks GB, Suissa S, Vandemheen KL, Doucette S, Maltais F, Bourbeau JF, Goldstein RS, Balter M, O’Donnell D, FitzGerald M.Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. Thorax 2008;63:122–128. DOI:10.1136/thx.2007.082636

Submitter declaration: I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment.

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Reply

We greatly appreciate the interest in our review, and would like to address the helpful feedback about potential limitations of the TORCH study.

1. Whilst 72 of the 6184 participants were excluded due to five sites that failed audits, the Supplemental Appendix 2 indicates that 'post-hoc analyses in which the 72 participants who were removed from the study were included did not materially change the outcome measures.' As these were exclusions, rather than participant withdrawals, it is appropriate that the data from these participants not be included in the mortality analysis, and that the study remains as intention to treat. For participants who were withdrawn, Appendix 2 states that 'For any subject who withdrew prematurely from the study, all available data up to the time of discontinuation were included in the analyses. Mortality data continued to be collected for subjects who withdrew early, up to 3 years after the start of study treatment.' As indicated in the feedback, the legend of Figure 1 of the paper states 'Adverse events included death during the study period but may not have included deaths occurring after patients withdrew from the study.' This reflects the reality of any clinical trial, in which data are available and included for analysis whilst participants are enrolled, and are often more difficult to collect once participants are withdrawn, despite the best efforts of the investigators. This is still within the scope of an intention to treat analysis. Imputation analysis gives wide confidence intervals for possible effects.
2. In their paper, the investigators provide a satisfactory and complete definition of exacerbation, as 'a symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these.' The protocol and paper do not describe that exacerbation data were collected after participant withdrawal.
3. Potential unblinding is a possibility in any study. However, this is not likely to substantially affect the performance of objective outcomes such as mortality and FEV1, or health-related outcomes such as exacerbations treated by antibiotics and/or steroids, or hospitalisation.
4. The investigators stated in advance that linguistically valid SGRQ versions would be analysed, and that the opportunity would be taken to prospectively validate SGRQ in countries without an existing validated version. The power calculation for the study was based on mortality, and therefore did not impact on the SGRQ analysis.
5. Our discussion interprets the pooled quality of life results as 'the magnitude of this benefit was relatively small (MD -1.22 units/year), compared to the minimum clinically significant difference of 4 units with the SGRQ.'

We have rated the attrition bias as low risk, as both of the ICS and placebo groups had similar rates of attrition. Given this and the other discussions above, we have maintained the current assessment of risk bias for the TORCH study in our review. Once again, we appreciate the detailed feedback that we have received for this review topic in an area of importance for COPD management.

Contributors

Feedback submitter lead: Alex Sykelyk, Pharmacy Resident, Lower Mainland Pharmacy Services, BC, Canada alexander.sykelyk@fraserhealth.ca Other contributors to feedback: Tanveer Brar, Natalie Baclawska, Kieran Shah, Aaron Tejani.

Ian Yang, the lead author of the review, responded to the feedback with support from the Cochrane Airways Feedback Editor, Christian Osadnik.

WHAT'S NEW

Date	Event	Description
25 August 2016	Feedback has been incorporated	Feedback received regarding evaluation of the TORCH study.

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 2, 2007

Date	Event	Description
29 July 2011	New search has been performed	Updated literature searches 2006 to 2011.
29 July 2011	New citation required and conclusions have changed	We added eight studies involving 3015 participants, strengthening the lung function result. 'Risk of bias' has been updated to the latest tool.

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Date	Event	Description
22 June 2008	New search has been performed	Converted to new review format.
6 January 2007	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Ian Yang, Toby Lasserson, Peter Black and Kwun Fong designed the initial review strategy and selected the studies for inclusion for the original 2007 version. Ian Yang, Esther Sim and Toby Lasserson extracted and entered the data for the original 2007 version.

Ian Yang and Melissa Clarke selected the studies for inclusion for the 2011 update, and extracted and entered the data for the 2011 update.

All current reviewers prepared the update of this review and approved its final version.

DECLARATIONS OF INTEREST

Ian Yang, Kwun Fong, Melissa Clarke, Esther Sim: none declared.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council, Australia.
- The Prince Charles Hospital Foundation, Australia.
- Cochrane Airways Group Scholarship, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage] [adverse effects]; Bronchial Hyperreactivity [drug therapy]; Bronchodilator Agents [*administration & dosage] [adverse effects]; Disease Progression; Forced Expiratory Volume [drug effects]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans

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