CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Regular inhaled short acting β_2 agonists for the management of stable chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis

F S F Ram, P Sestini

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See end of article for authors' affiliations

Correspondence to: Dr F S F Ram, St George's Hospital Medical School, Department of Physiological Medicine, Cranmer Terrace, London SW17 0RE, UK; fram@sghms.ac.uk

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Background: Despite the lack of reversibility, patients with chronic obstructive pulmonary disease (COPD) often report symptomatic improvement with inhaled short acting β_2 agonist bronchodilators (ISABAs) in the management of both stable and acute exacerbations of COPD. A review of the literature was undertaken to determine the effectiveness of regular treatment with ISABAs compared with placebo in stable COPD.

Methods: A search for randomised controlled trials was carried out using the Cochrane Collaboration database of trials up to and including May 2002.

Results: Thirteen studies of 7 days to 8 weeks in duration on 237 patients aged 56–70 years with forced expiratory volume in 1 second (FEV_1) 60–70% predicted were included in the review. All studies used a crossover design with adequate washout periods and were of high methodological quality. ISABA was delivered either through a nebuliser or a pressurised metered dose inhaler. Spirometric tests performed at the end of the study and after the treatment (post-bronchodilator) showed a slight but significant increase in FEV_1 and forced vital capacity (FVC) compared with placebo. In addition, both morning and evening peak expiratory flow rate (PEFR) were significantly better during active treatment than during placebo. An improvement in the daily breathlessness score was observed with ISABA treatment. The risk of treatment failure was reduced by more than 50% with ISABA. Preference for ISABA was nine times higher than for placebo.

Conclusions: Use of ISABA on a regular basis for at least 7 days in patients with stable COPD is associated with improvements in post-bronchodilator lung function and decreases in both breathlessness and treatment failure. This review has shown that regular administration of ISABAs is an effective and inexpensive treatment for the management of patients with stable COPD.

Chronic obstructive pulmonary disease (COPD) is a condition characterised by progressive airflow limitation that is, at most, partially reversible. Despite the lack of reversibility, patients often report symptomatic improvement with inhaled short acting β_2 agonist bronchodilator (ISABA) medications. These agents are widely used and are recommended in guidelines for the management of COPD.[1–4] ISABAs are used either on an "as required" or "regular plus as required" basis and may be used in conjunction with other bronchodilators such as ipratropium and methylxanthines. ISABAs are used in the management of both chronic stable COPD and acute exacerbations. They can be delivered in several ways—for example, by metered dose inhaler, dry powder inhaler, or by nebulisation. This review examines the effectiveness of inhaled ISABAs compared with placebo in the management of stable COPD.

METHODS

Types of studies and participants

Only randomised controlled trials were considered for inclusion. Subjects included in the trials were all adults with stable COPD as defined by internationally accepted guidelines.[2–4]

Types of interventions

In all the studies included in the review ISABAs were given by inhalation for at least 7 days and compared with placebo. Data from trials where ISABAs were used alone or in combination with other medicines (such as ipratropium bromide) were used only if there was direct comparison between ISABA and placebo alone.

Search strategy

Randomised controlled trials (RCTs) were identified without any language restrictions using the Cochrane Collaboration trials register. This register contains searches from many electronic sources (for example, Medline, Embase, Cinahl, Science Citation). It also includes results of manual hand searching of journals and conference abstracts as well as details of unpublished and ongoing studies. This database was searched using the following terms: salbutamol *or* albuterol *or* terbutaline *or* isoproterenol *or* reproterol *or* fenoterol *or* orciprenaline *or* metaproterenol *or* ((beta* *and* agonist*) *and* short)) *or* (bronchodilator* *and* short). In addition, the reference lists of review articles and RCTs retrieved in full were searched for other potentially relevant citations.

Selection of studies

Abstracts of articles identified using the above search strategy were viewed and articles that appeared to fulfil the inclusion criteria were retrieved in full. All single dose studies were excluded. From the full text of the remaining articles, two reviewers independently established whether each study met the inclusion criteria as a randomised placebo controlled trial of regular ISABA in stable COPD for at least 7 days or more. Percentage agreement between the two reviewers was recorded and disagreement was resolved with discussion. Authors of all included studies were contacted for clarification regarding abstracted data and methodological issues.

Data was abstracted and entered into RevMan 4.1 (Cochrane Collaboration software). Each entry was double checked by both reviewers.

Table 1 Characteristics of studies included in the review

Study reference	Participants	Intervention
Dullinger *et al*[9]	10 men with slowly progressive exertion, FEV_1 <1.5 l with no documented history of asthma	1 week treatment with metaproterenol, 1.3 mg from a metered dose canister or placebo six times a day and oral theophylline or placebo. Washout period details not reported
Guyatt *et al*[5]	27 men with FEV_1 <70% predicted and FEV_1/VC ratio <0.7. Less than 25% increase in FEV_1 after salbutamol	2 week treatment with inhaled salbutamol 200 µg four times a day and/or oral theophylline. For washout period the authors excluded first 3 days' data from the analysis
Guyatt *et al*[6]	32 men with greater or less than 25% increase in FEV_1 after salbutamol	2 week treatment with inhaled salbutamol 200 µg four times a day and/or oral theophylline. Excluded first 3 days' data
Guyatt *et al*[7]	32 men with greater or less than 25% increase in FEV_1 after salbutamol	2 week treatment with inhaled salbutamol 200 µg four times a day and/or oral theophylline. Excluded first 3 days' data
Hansen *et al*[12]	48 patients (24 men) with history of chronic bronchitis, FEV_1 <1 litre, never treated with a nebuliser or oxygen at home	5 mg terbutaline or placebo from a nebuliser twice daily for 2 weeks. Washout was 2 week run in period
Jaeschke *et al*[8]	24 patients (same who completed Guyatt *et al*[7])	2 week treatment with inhaled salbutamol 200 µg four times a day and/or oral theophylline. Excluded first 3 days' data
Klock *et al*[10]	15 patients (12 men) with ATS 1962 criteria for chronic bronchitis and FEV_1 <65% predicted	3 week period of 20 sprays (1 mg) of 1:100 atropine sulphate, 1:100 isoproterenol HCl, or placebo four times a day from a nebuliser. Washout period 2 weeks
Light *et al*[11]	16 patients with FEV_1 <2 l, FEV_1/FVC ratio <50%	8 week period of isoproterenol 250 mg or placebo from nebuliser four times a day. Washout period 2 weeks
Shah *et al*[16]	12 patients with COPD (mean FEV_1 0.6 l) and <15% reversibility on spirometry	1 week treatment with 200 µg salbutamol 4-hourly or placebo from metered canister. Washout period 1 week
Silins *et al*[13]	8 men with severe airflow limitation due to COPD, previously on chronic treatment with inhaled β_2 agonist	Four 1-week periods, 2 with terbutaline 5 mg four times a day and 2 with placebo from nebuliser. Washout period 1 week
Tandon *et al*[14]	37 men with a history of chronic bronchitis, FEV_1 <65% predicted in the past 2 years	6 week treatment with 4 puffs terbutaline (1 mg) four times a day and oral theophylline twice a day. Washout period 2 weeks
Taylor *et al*[17]	25 patients (21 men) with chronic bronchitis and >10% improvement in FEV_1 after salbutamol	Four 3-week periods with 200 µg salbutamol or placebo four times a day from metered canisters and/or oral theophylline twice a day. Excluded first 3 days' data
Wilson *et al*[15]	10 patients (9 men) with severe chronic airway obstruction and marked dyspnoea not improved after high dose oral steroids	2 week periods with 5 mg salbutamol or placebo four times a day from a nebuliser. Washout not discussed

FEV_1=forced expiratory volume in 1 second; VC=vital capacity.

Study quality assessment

Study quality was assessed using the Cochrane Collaboration approach to assessment of allocation concealment. All trials were scored and entered using the following principles: grade A=adequate concealment, grade B=uncertain, grade C=clearly inadequate concealment, and grade D=no attempt at allocation concealment.

Data analysis

Data were analysed as either continuous or dichotomous outcomes using standard statistical techniques. For continuous outcomes the weighted mean difference (WMD) or the standardised mean difference (SMD) and 95% confidence intervals were calculated. For dichotomous outcomes the relative risk (RR) or odds ratio (OR) was calculated with 95% confidence intervals. Tests for heterogeneity was conducted for all outcomes. If significant heterogeneity was found and not explained by study quality, a priori defined subgroup analyses included type of ISABA, dose and delivery system, study duration, severity of COPD, setting of study, age of patients, and concomitant medication.

RESULTS

Trial searches and study characteristics

The bibliographic search yielded 405 references. Of these, 311 were identified by the title and abstract alone to involve diseases different from COPD, were studies that used oral rather than inhaled ISABA, or included patients with acute exacerbations. The full text of the remaining 94 papers was obtained and examined, together with another seven papers identified from the reference list of these full papers and five papers previously known by the reviewers. From these 106 papers, 57 reported the effects of chronic treatment with inhaled ISABA in patients with stable COPD; 44 of these were excluded, mostly because of the lack of a comparative placebo group, leaving 13 studies with 237 patients aged 56–70 for inclusion in the review. There was total agreement between the two independent reviewers on inclusion of studies and Cochrane study quality grading. Four of the included studies[5–8] were reports related to the same cohort of patients, so only one of these studies was included as the key reference in the analysis. The treatments consisted of isoproterenol in three of the included studies,[9–11] terbutaline in another three,[12–14] and salbutamol in the remaining studies. Four studies used nebulisers for administering ISABA[11–13 15] while the others used pressurised metered dose inhalers or other portable hand held inhaler devices. Patients were exclusively or mostly male in all studies except one[12] where 50% of the patients were female.

All included studies were of 1–8 weeks duration, were randomised double blind placebo controlled trials, and used a crossover trial design. Six of the included studies had a

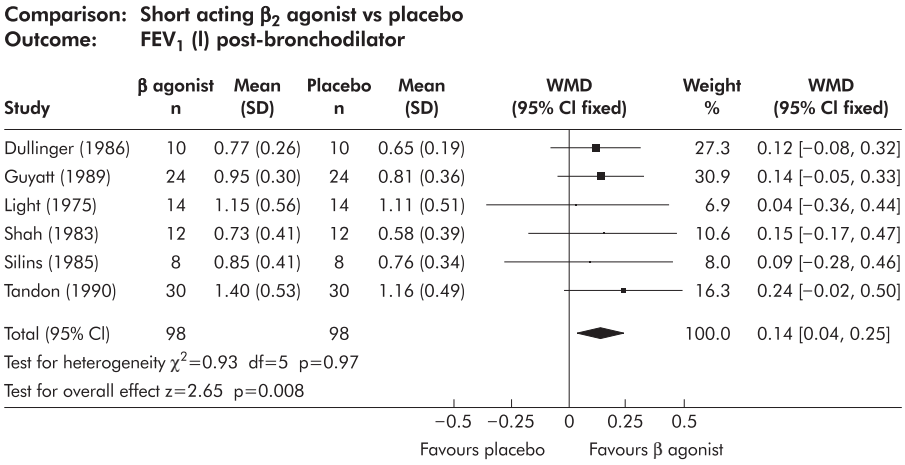

Figure 1 Post-bronchodilator forced expiratory volume in 1 second (FEV_1) in litres. A square box indicates the mean value for each trial with the line through it representing the 95% confidence interval (CI). Mean values left of the zero effect line (0) favour placebo and values to the right favour regular β_2 agonist use. The solid diamond indicates the overall (all studies combined) mean effect of regular β_2 agonist use on post-bronchodilator FEV_1. A percentage weighting (Weight %), which is dependent on the precision and sample size of the estimation of the mean value, is allocated to each study. The χ^2 (0.93) and degrees of freedom (df = 5) values at the bottom left of the graph provide a measure of heterogeneity of the combined results that contributed towards the overall mean result for post-bronchodilator FEV_1. The Z statistic (2.65) indicates the level of significance of the overall result.

washout period of more than 1 week between the crossover arms,[10–14 16] three studies did not use a washout period but excluded data from the first 3 days of each arm in their analysis,[5 8 17] and two studies did not discuss details of the washout period.[9 15] A possible pitfall of crossover studies is the presence of carryover effects from the first treatment into the second treatment period, leading to an underestimation of the real difference between treatments.[18] However, in all the studies included in the review, chronic treatment with ISABA did not seem to alter pre-bronchodilator respiratory function, which suggests that carryover effects are unlikely to have occurred in these studies despite their crossover design and, as most studies included a washout period or allowed for it by excluding data, this is unlikely to have been a problem. Further details of the included studies are shown in table 1.

Spirometric testing

Spirometric tests performed after administration of ISABA (post-bronchodilator) at the end of the treatment period improved both forced expiratory volume in 1 second (FEV_1) (WMD 0.140 l, 95% CI 0.04 to 0.25) and forced vital capacity (FVC) (WMD 0.30 l, 95% CI 0.02 to 0.58) slightly but significantly when compared with placebo (figs 1 and 2). Spirometric tests performed at the end of the treatment period and before administration of ISABA (pre-bronchodilator) showed no significant difference in FEV_1 or FVC. Many of the studies did not measure functional residual capacity (FRC), total lung capacity (TLC), or residual volume (RV) at the end of the study period, and those that did made these measurements several hours after treatment. The results for FRC, TLC, and RV were not significantly different between the ISABA and placebo groups ($p>0.05$ in all cases), possibly because of the small number of studies and patients contributing data towards these outcomes.

Peak flow rate

Post-bronchodilator morning and evening peak expiratory flow rate (PEFR) was significantly higher in the treatment group than in the placebo group (morning: WMD 29.17 l/min, 95% CI 0.25 to 58.09; evening: WMD 36.75 l/min, 95% CI 2.56 to 70.94). In addition to the studies included in the meta-analysis, Hansen *et al*[12] reported a significant increase ($p=0.0001$) in PEFR during active treatment when compared with placebo (11% and 5% in the morning, 8% and 3% in the evening, respectively). Shah *et al*[16] reported a significant increase in mean daily PEFR from 157 l/min during placebo to 182 l/min while on salbutamol (signed rank test). As previously observed for spirometric tests, no significant differences were noted when PEFR was recorded before bronchodilator treatment.

Breathlessness scores

Four studies used previously validated breathlessness scales which included the seven point Likert scale[9 12 16] and the

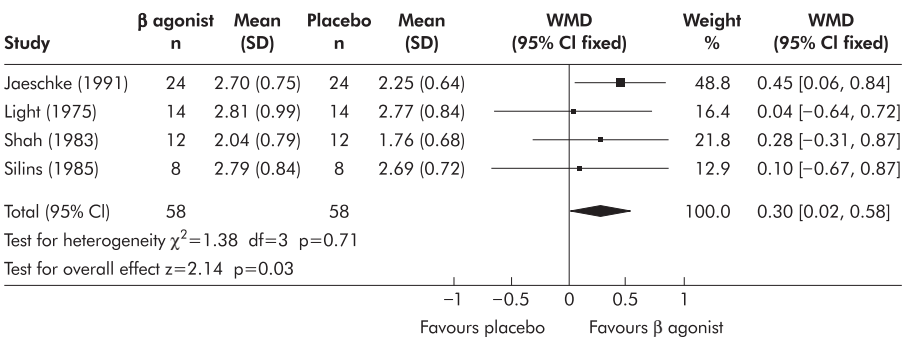

Figure 2 Post-bronchodilator forced vital capacity (FVC) in litres.

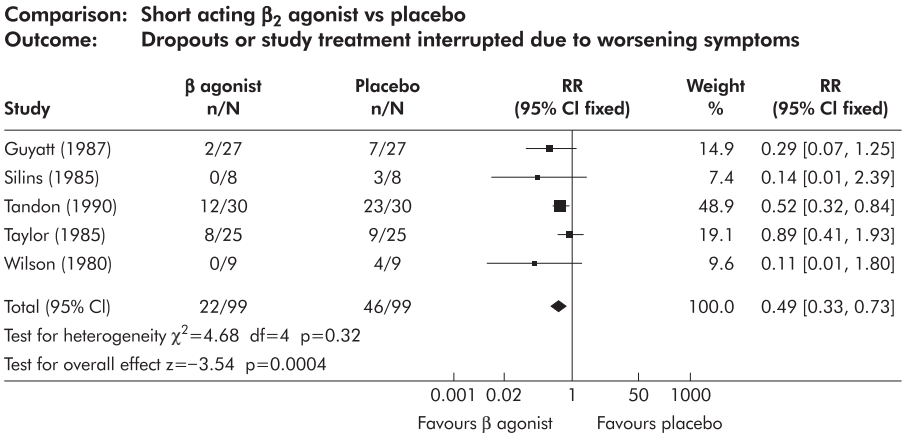

Figure 3 Treatment failure, defined as the number of patients dropping out of the study due to worsening symptoms.

100 mm visual analogue scale.[6] When the results from these four studies were combined a significant improvement in daily breathlessness score was observed during treatment with ISABA (SMD 1.33, 95% CI 1.01 to 1.65). Two studies used a simple (0–3 point non-validated) scale[13 15] and reported morning and evening breathlessness scores which did not change significantly after treatment with ISABA. Studies that failed to present their data for breathlessness in a suitable form for inclusion in the analysis reported no difference in dyspnoea scores between active treatment and placebo.

Treatment failure

Five studies[5 13–15 17] reported the number of patients who dropped out from their study because of worsening dyspnoea during treatment with ISABA or placebo (fig 3). The risk of treatment failure was significantly greater in the placebo group than in the ISABA group (RR 0.49, 95% CI 0.33 to 0.73).

Patient preference

Four studies[11–13 15] reported patient preference (fig 4), which showed that patients were almost nine times more likely to prefer ISABA to placebo (OR 9.04, 95% CI 4.64 to 17.61).

Subgroup analysis and tests for heterogeneity

Studies included in the review were subgrouped according to a priori defined criteria (type of ISABA, dose and delivery system, study duration, severity of COPD, study setting, age of patients, and concomitant medication). There were no significant differences between these subgroups or any evidence of heterogeneity, so studies were combined to provide an overall effect size.

Sufficient data were not reported in the included studies on the following outcome measurements: hospital admissions, mortality, adverse effects, progressive cycle ergometry, distance walked, rescue medication usage, sputum production, or cough.

DISCUSSION

This review has shown that ISABAs used on a regular basis for at least 7 days in patients with moderate to severe COPD are associated with an improvement in post-bronchodilator lung function and a decrease in symptoms of breathlessness. Patients are also more likely to prefer treatment with ISABA than placebo, and are less likely to fail or to drop out from treatment.

Despite the great number of patients with COPD currently being treated with ISABAs, we found few studies suitable for inclusion in our review. Because of the small number and size of controlled trials, it was difficult to evaluate the real benefit or adverse effects afforded by ISABAs in COPD. The small number of studies found for this review suggests that ISABAs have gained popularity in the treatment of stable COPD from the results of acute studies and from uncontrolled clinical trials, as well as from a perception of benefit by patients and treating physicians.

Although we restricted our analysis to typical COPD patients as defined by internationally accepted criteria,[1–4] the study populations were varied in terms of severity and acute bronchodilator response. Despite these differences, the results were consistent across the many studies. The findings of this review should therefore be applicable to most patients with COPD, excluding those with mild COPD or with characteristics of asthma.

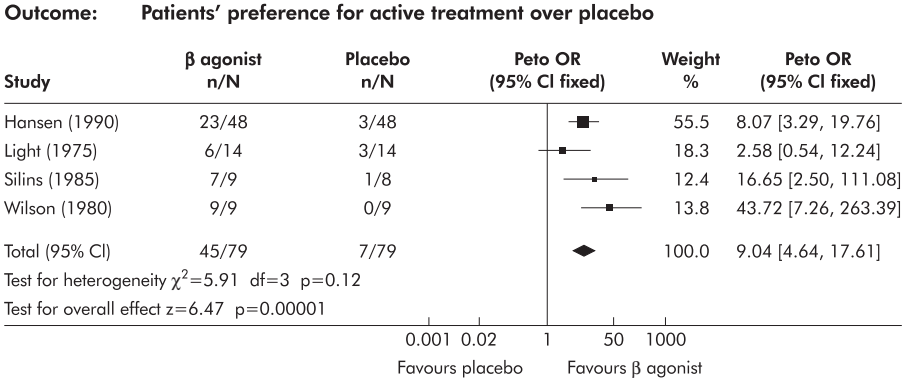

Figure 4 Patient preference for short acting β_2 agonists or placebo.

Unlike pre-bronchodilator respiratory function, post-bronchodilator FEV_1 improved significantly ($p=0.008$) but slightly (140 ml) after active treatment compared with placebo. This observation confirms the bronchodilator effect of ISABA treatment in COPD observed in several acute studies.[19–22] None of the included studies was designed to investigate changes in bronchodilator activity over time, and our data show no evidence for the hypothesis that this activity is attenuated by chronic treatment with ISABA. The short duration of the included studies in this review made them unsuitable for evaluating any effect on disease progression over time.

Analysis of PEFR data confirms that the improvement in respiratory function after regular ISABA persists during the day and throughout the treatment period. Similarly, the improvement in daily breathlessness scores indicates that most patients with COPD gain significant benefit from ISABA throughout treatment. Although we were forced to combine breathlessness scores using standardised means to overcome the different scales used in the included studies, it should be noted that the improvement in the score was consistent across studies. Therefore, although the size of the improvement cannot be exactly estimated using this combined score, this effect is likely to be clinically significant.

Patient preference and treatment failure rate favoured ISABA treatment, although patient selection could have biased the results of some of the trials. For instance, most of the patients in three studies[13–15] were already on chronic treatment with nebulised bronchodilators which would make these patients unlikely not to respond to this treatment. It is not surprising that these patients had a greater preference for active treatment and more dropouts during placebo. In contrast, in the study by Hansen *et al*[12] which excluded patients who had previously been treated with a nebuliser at home, 23 patients preferred terbutaline, three preferred placebo, six preferred the run in period, and the remaining 16 had no preference. Although it is clear that in this study active treatment was superior to placebo, it was surprising to see that only 23 of 48 patients (less than 50%) preferred terbutaline.

This review did not include comparison with alternative treatments such as long acting β_2 agonists, anticholinergic agents, or combinations of a β_2 agonist with an anticholinergic drug. Several recent clinical trials indicate that chronic treatment with inhaled long acting β_2 agonists such as salmeterol or formoterol is effective in improving clinical conditions and quality of life in COPD.[23] Because of their longer action, these drugs may provide better coverage over day and night time, and therefore may prove more effective than the short acting drugs considered in this review. Furthermore, a recent well controlled trial has indicated that chronic inhaled treatment with both ipratropium bromide and salbutamol is no more effective than treatment with chronic ipratropium bromide alone plus inhaled salbutamol on an "as needed" basis.[24] It can therefore be concluded that several effective treatments are currently available and, while a direct comparison between all of them is not available, a choice can be made based on individual response, preferences, and economical convenience or constraints.

Large parallel long term studies are needed to investigate the effectiveness of regular inhaled β_2 agonists, possibly in comparison with anticholinergics, on the frequency of exacerbations, occurrence of adverse effects, and any possible effect on the progression of the disease, in patients with or without a clinical response to acute bronchodilator treatment. Because of the introduction of long acting β_2 agonists, studies are more likely to be conducted using these agents. However, this review has shown that regular administration of ISABAs remains an effective and inexpensive treatment for the management of patients with stable COPD.

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Authors' affiliations
F S F Ram, St George's Hospital Medical School, Department of Physiological Medicine, University of London, UK
P Sestini, University of Sienna, Department of Clinical Medicine and Immunological Sciences, Italy

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