Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial

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Summary

Background Inhaled longacting β_2 agonists improve lung function and health status in symptomatic chronic obstructive pulmonary disease (COPD), whereas inhaled corticosteroids reduce the frequency of acute episodes of symptom exacerbation and delay deterioration in health status. We postulated that a combination of these treatments would be better than each component used alone.

Methods 1465 patients with COPD were recruited from outpatient departments in 25 countries. They were treated in a randomised, double-blind, parallel-group, placebo-controlled study with either 50 µg salmeterol twice daily (n=372), 500 µg fluticasone twice daily (n=374), 50 µg salmeterol and 500 µg fluticasone twice daily (n=358), or placebo (n=361) for 12 months. The primary outcome was the pretreatment forced expiratory volume in 1 s (FEV_1) after 12 months treatment' and after patients had abstained from all bronchodilators for at least 6 h and from study medication for at least 12 h. Secondary outcomes were other lung function measurements, symptoms and rescue treatment use, the number of exacerbations, patient withdrawals, and disease-specific health status. We assessed adverse events, serum cortisol concentrations, skin bruising, and electrocardiograms. Analysis was as predefined in the study protocol.

Findings All active treatments improved lung function, symptoms, and health status and reduced use of rescue medication and frequency of exacerbations. Combination therapy improved pretreatment FEV_1 significantly more than did placebo (treatment difference 133 mL, 95% CI 105–161, p<0·0001), salmeterol (73 mL, 46–101, p<0·0001), or fluticasone alone (95 mL, 67–122, p<0·0001). Combination treatment produced a clinically significant improvement in health status and the greatest reduction in daily symptoms. All treatments were well tolerated with no difference in the frequency of adverse events, bruising, or clinically significant falls in serum cortisol concentration.

Interpretation Because inhaled long-acting β_2 agonists and corticosteroid combination treatment produces better control of symptoms and lung function, with no greater risk of side-effects than that with use of either component alone, this combination treatment should be considered for patients with COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity worldwide. It is characterised by chronic progressive symptoms, airflow obstruction,[1,2] and impaired health status,[3] which is worse in those who have frequent, acute episodes of symptom exacerbation.[4] The aim of treatment is to prevent and control symptoms and exacerbations while improving lung function and health status.[5,6] Any new treatment approach should be judged against these endpoints.

Inhaled long-acting β_2 agonists improve airflow obstruction, control of symptoms, and health status in patients with COPD over 3–4 months[7–14] and have several potentially beneficial non-bronchodilatory effects.[15] The role of inhaled corticosteroids in COPD management is less certain.[16] These drugs do not change the rate of decline in lung function,[17–20] but can increase postbronchodilator forced expiratory volume in 1 s (FEV_1),[17,19] reduce the number of exacerbations,[17,18] and slow the rate of decline in health status.[17] Whether long-acting β_2 agonists and inhaled corticosteroids in combination will result in treatment effects that are better than those associated with either drug alone is not clear. Furthermore, we do not know whether improvements seen in the short term will be maintained during sustained treatment. To test our hypothesis, we did a randomised controlled trial over 1 year of combination treatment with salmeterol and fluticasone versus each of the components and placebo.

Methods

Patients

We recruited outpatients with COPD from 196 hospitals in 25 countries. All patients had a baseline FEV_1 before bronchodilation that was 25–70% of that predicted, an increase of less than 10% of predicted FEV_1 30 min after inhaling 400 µg salbutamol, and a prebronchodilator FEV_1/forced vital capacity (FVC) ratio of 70% or less.[21] Patients also had a history of at least 10 pack-years of smoking (ie, equivalent to 20 cigarettes smoked per day for 10 years), of chronic bronchitis, at least one episode of acute COPD symptom exacerbation per year in the previous 3 years, and at least one exacerbation in the year immediately before trial entry that required treatment with oral corticosteroids, antibiotics, or both.

We excluded patients who had respiratory disorders other than COPD, required regular oxygen treatment, or had received systemic corticosteroids, high doses of inhaled corticosteroids (>1000 µg daily beclometasone dipropionate, budesonide, or flunisolide or >500 µg daily fluticasone), or antibiotics in the 4 weeks before the 2 week run-in period before the trial began.

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
Withdrawal after randomisation	140 (39 %)	119 (32 %)	108 (29 %)*	89 (25 %)†‡
Age	63·4 (8.6)	63.2 (8.6)	63.5 (8.5)	62.7 (8.7)
Male	269 (75 %)	261 (70 %)	260 (70 %)	270 (75 %)
Current smoker	171 (47 %)	191 (51 %)	198 (53 %)	186 (52 %)
Pack-years smoked	43·4 (22·4)	43·7 (21·9)	41·5 (20·7)	42·0 (22·4)
Previous ICS use	188 (52 %)	183 (49 %)	202 (54 %)	178 (50 %)
Previous LABA use	136 (38 %)	156 (42 %)	148 (40 %)	151 (42 %)
Pretreatment FEV_1 (% predicted)	44·2 (13·7)	44·3 (13·8)	45·0 (13·6)	44·8 (14·7)
Reversibility (% predicted FEV_1)	4·0 (4·5)	3·7 (4·3)	3·7 (3·9)	4·0 (4·7)
Pretreatment FEV_1 (mL)	1266 (467)	1245 (452)	1260 (449)	1308 (532)
Postbronchodilator FEV_1 (mL)	1379 (476)	1346 (463)	1363 (460)	1419 (549)
Pretreatment FVC (mL)	2500 (800)	2386 (751)	2443 (781)	2537 (838)
PEF L/min	243 (89)	235 (90)	246 (90)	247 (93)
SGRQ score	47·1 (16·5)	48·7 (17·1)	49·8 (15·8)	47·1 (15·7)
Median use of relief medication per day (range)	2·7 (0–17)	2·9 (0–14)	2·8 (0–15)	2·7 (0–11)
Mean number awakenings per week	3·5 (5·3)	3·5 (6·1)	3·5 (4·9)	2·8 (4·9)

ICS=inhaled corticosteroids. LABA=longacting β2 agonist. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. PEF=peak expiratory flow. SGRQ=St George's Respiratory Questionnaire. Data are number (%) or mean (SD) unless otherwise indicated. *p=0·007 *vs* placebo. †p=0·0001 *vs* placebo. ‡p=0·033 *vs* salmeterol.

Table 1: **Patients' demographic data and baseline characteristics**

We obtained approval from local ethics committees at each participating site, and all patients provided written informed consent.

Study design

We used a randomised, double-blind, placebo-controlled, parallel-group design. Recruited patients participated in a 2-week run-in to the trial, a 52-week treatment period with clinic visits at weeks 0, 2, 4, 8, 16, 24, 32, 40, and 52, and a 2-week post-treatment follow-up.

We used a randomisation schedule generated by the patient allocation for clinical trials (PACT) program to assign patients to study treatment groups. Every participating centre was supplied with a list of patient numbers (assigned to patients at their first visit) and a list of treatment numbers. Patients who satisfied the eligibility criteria were assigned the next sequential treatment number from the list. Salmeterol and fluticasone combination (50/500 μg twice daily), salmeterol (50 μg twice daily), fluticasone (500 μg twice daily) and placebo were packaged in identical inhaler devices. Study drugs were labelled in a way to ensure that both the patient and the investigator were unaware of the allocated treatment .

During the 2-week run-in, patients stopped taking regular inhaled corticosteroids or long-acting β_2 agonists. Inhaled salbutamol was used as relief medication throughout the study, and regular treatment with anticholinergics, mucolytics, and theophylline was allowed. All non-COPD medications could be continued if the dose remained constant whenever possible, and if their use would not be expected to affect lung function. If patients had clinically stable symptoms after 2 weeks, they were randomised to receive one of the following treatments: 50 μg salmeterol and 500 μg fluticasone in combination; 50 μg salmeterol; 500 μg fluticasone; or placebo, all twice daily, for 52 weeks via a multidose dry-powder inhaler (Diskus or Accuhaler [GlaxoSmithKline, Greenford, UK]).

The primary efficacy measure was FEV_1 after patients had abstained from all bronchodilators for at least 6 h, and from study medication for at least 12 h. Lung-

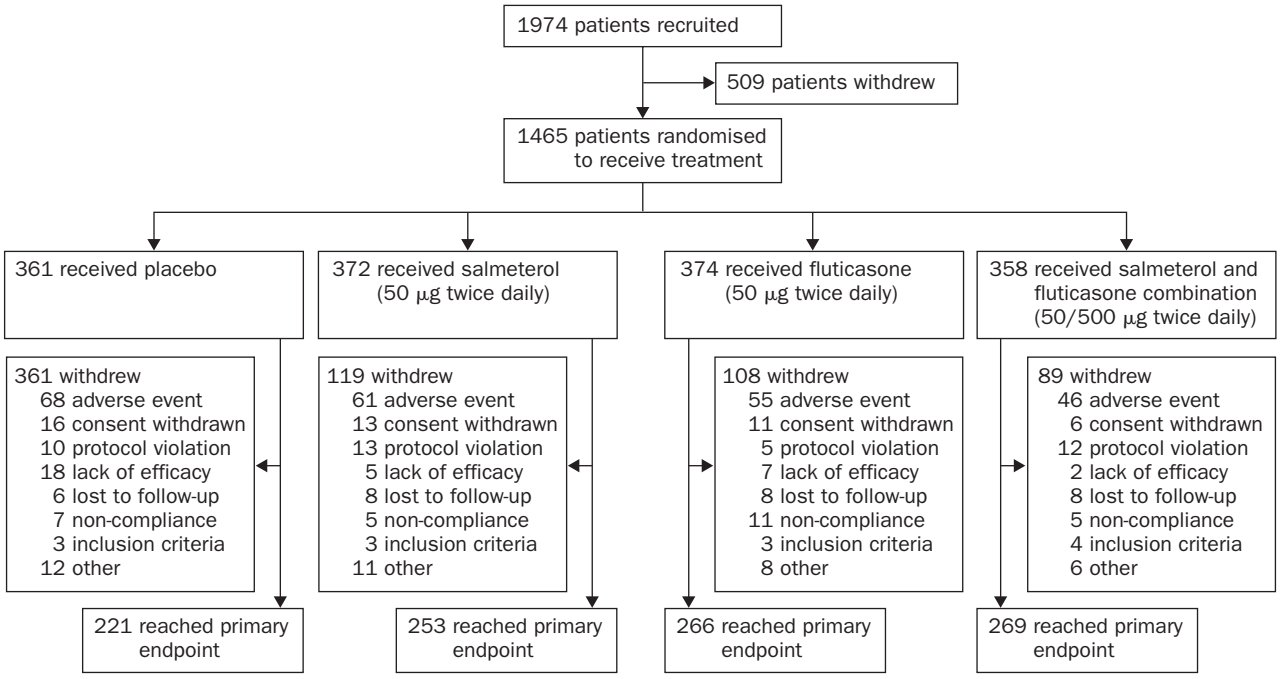

Figure 1: **Trial profile**

function tests were done in the clinic: pretreatment FVC, and postbronchodilator FEV_1 and FVC were measured at each visit. Postbronchodilator measurements were made 30 min after inhalation of 400 µg of salbutamol. All spirometry measurements were done at the same time of day for all patients, with the same spirometer. Every morning, patients used daily record cards to record the highest of three peak expiratory flow values measured with a mini-Wright peak flow meter (Clement Clarke International Harlow, UK) before medication.

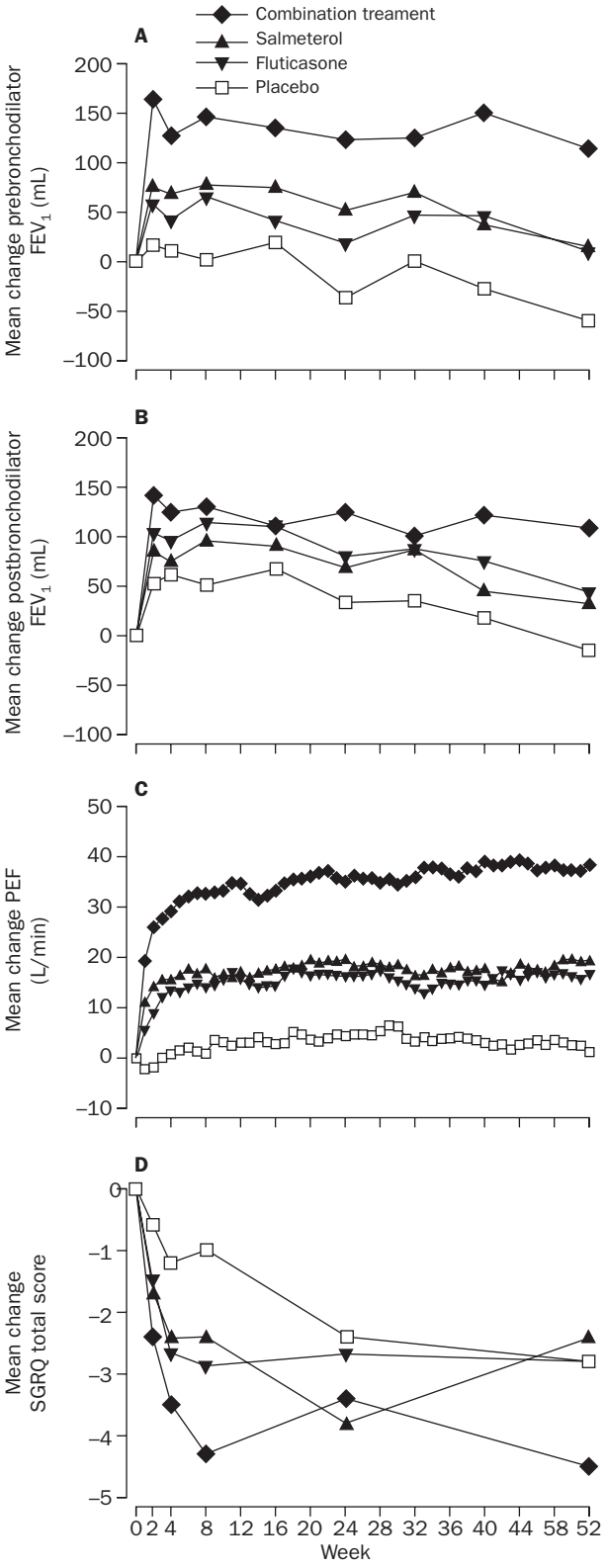

Figure 2: **Effect of treatment on lung function measurements and health status**

Raw mean changes from baseline are shown. A, prebronchodilator FEV_1. B, postbronchodilator FEV_1. C, daily peak expiratory flow. D, health status—the fall in St George's score represents an improvement in health status.

Every morning, patients recorded the number of times they used relief medication, their symptom scores, and the number of night-time awakenings for the previous 24 h. Symptoms were scored as: breathlessness, 0 (none) to 4 (breathless at rest); cough, 0 (none) to 3 (severe); sputum production, 0 (none) to 3 (severe); sputum colour, 0 (no sputum produced) to 4 (dark yellow or green).

The occurrence of acute exacerbations of COPD symptoms was investigated at every clinic visit. Exacerbations were defined a priori as a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both. Episodes that required corticosteroid treatment or hospital admission were noted separately. Health status was assessed with the St George's Respiratory Questionnaire at weeks 0, 2, 4, 8, 24, and 52. In the 22 non-English speaking countries we used a validated translation of this questionnaire.

Adverse event information was obtained at every clinic visit by recording spontaneously reported complaints from patients and asking general questions about medical troubles and concomitant medication. Morning (0800–1000 h) cortisol concentrations in serum were measured after fasting at weeks 0, 24, and 52. At every visit we noted the number of bruises on the volar side of the forearms that had a diameter greater than 5 cm. All patients had 12-lead electrocardiography at weeks 0, 24, and 52, and investigators categorised the results as normal, abnormal but not clinically significant, or abnormal and clinically significant.

Statistical analysis

We estimated that a sample size of 300 patients per treatment group would be needed to obtain data for 250 patients so as to detect a 0·10 L difference in FEV_1 at the 5% significance level with 90% power, assuming an SD of 0·35 L for FEV_1. We analysed pretreatment FEV_1 using repeated measures analysis.[22] Time was included as a categorical parameter and an unstructured variance-covariance matrix was fitted with SAS proc mixed software version 6.12. We also used these methods to analyse other lung function variables and questionnaire scores. We analysed log-transformed serum cortisol concentrations, morning peak expiratory flow, and mean symptom score during weeks 1–52 using analysis of covariance. The number of exacerbations was analysed by a maximum likelihood Poisson regression, with the amount of time a patient had had treatment as an offset variable. Covariates used for analyses, where applicable, were age, sex, country, baseline value (such as FEV, and FVC at randomisation), and smoking status. Interactions of treatment with all covariates were tested for pretreatment FEV_1, exacerbations, and health status questionnaire scores. For use of rescue medication, the median data for weeks 1–52 were analysed using the van Elteren extension to the Wilcoxon rank sum test,[23] stratified by smoking status, and the confidence limits calculated with the Hodges-Lehman method.[24] The number of withdrawals was analysed with the Cochran-Mantel-Haenszel test, stratified by smoking status, and time to withdrawal was analysed with Cox's proportional hazards model.

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
Pretreatment FEV_1 (mL)				
Adjusted mean	1264 (11)	1323 (11)*	1302 (11)†	1396 (11)
Treatment difference‡	133	73	95	
(95% CI)	(105–161)	(46–101)	(67–122)	
p‡	<0·0001	<0·0001	<0·0001	
Postbronchodilator FEV_1 (mL)				
Adjusted mean	1408 (11)	1436 (11)	1454 (11)§	1484 (11)
Treatment difference‡	76	48	31	
(95% CI)	(47–106)	(19–77)	(2–60)	
p‡	<0·0001	0·0014	0·039	
Pretreatment FVC (mL)				
Adjusted mean	2439 (19)	2525 (19)¶	2500 (18)‖	2594 (19)
Treatment difference‡	155	68	94	
(95% CI)	(106–204)	(20–117)	(46–142)	
p‡	<0·0001	0·006	<0·0001	
PEF (L/min)				
Adjusted mean	242 (2·1)	257 (2·0)*	255 (2·0)*	274 (2·1)
Treatment difference‡	32	17	18	
(95% CI)	(26–37)	(11–22)	(13–24)	
p‡	<0·0001	<0·0001	<0·0001	

Data are mean (SE). *p<0·0001 *vs* placebo; †p=0·0063 *vs* placebo; ‡vs combination treatment §p=0·002 *vs* placebo; ¶ p=0·0004 *vs* placebo; ‖ p=0·013 *vs* placebo.

Table 2: **Effect of 52 weeks' treatment on lung function**

Role of the funding source

The study sponsor, GlaxoSmithKline, was involved together with the principal investigators in the study design; the collection and analysis of data, which was made freely available to all the principal investigators; and the decision to submit the paper for publication.

Results

We recruited 1974 patients from 196 centres in 25 countries, of whom 1465 received treatment (figure 1). Demographic data, baseline characteristics, and compliance did not differ between groups, but the withdrawal rate did. Significantly fewer patients withdrew from the combination and fluticasone groups than from placebo and salmeterol groups (table 1). The main reason for differences in withdrawal was presence of adverse events. Patients in the combination group had a slightly higher mean prebronchodilator and postbronchodilator FEV_1 and fewer mean awakenings per week than did those in other groups. These minor imbalances in baseline data were accounted for in the statistical analyses since both baseline FEV_1 and mean night awakenings per week were used as covariates in analyses where appropriate.

The three active treatments increased pretreatment FEV_1 significantly compared with placebo (salmeterol/fluticasone p<0·0001; salmeterol p<0·0001; fluticasone p=0·0063; figure 2). This improvement was evident by week 2 and was sustained throughout treatment. The rise in FEV_1 associated with combination therapy was significantly greater than with either of its components separately (table 2, figure 2). By week 52, pretreatment FEV_1 in the combination group had increased by 10% compared with 2% in both the salmeterol and fluticasone groups, and had fallen by 3% in the placebo group. We noted the same trend for the other lung-function variables (figure 2). The treatment-by-smoking-status interaction for prebronchodilator FEV_1 was not significant (p=0·134), indicating that the difference between the treatment groups was unaffected by whether the participant continued to smoke, or not. Furthermore, the effects of treatment were not biased by unbalanced changes in smoking status between the treatment groups. During the 12-month study period, a total of 103 patients (6–7% in each treatment group) changed their smoking habit, with most of these giving up smoking.

Compared with placebo, all active treatments significantly reduced the number of exacerbations per patient per year and the number of exacerbations that needed treatment with oral corticosteroids (table 3). The rate of exacerbations fell by 25% in the combination group (p<0·0001) and by 20% (p=0·0027) and 19% (p=0·0033) in the salmeterol and fluticasone groups, respectively, compared with placebo. The treatment effect was more pronounced in patients with severe disease (ie, a baseline FEV_1 <50% of predicted), who showed a 30% reduction with the

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
Total exacerbation rate				
Mean rate per patient per year (SD)	1·30	1·04*	1·05*	0·97
Treatment ratio† (95% CI)	0·746	0·930	0·925	
	(0·643–0·865)	(0·801–1·080)	(0·797–1·073)	
p†	<0·0001	0·345	0·304	
Rate of exacerbations requiring oral corticosteroids				
Mean rate/patient/year	0·76	0·54‡	0·50§	0·46
Treatment ratio†	0·607	0·853	0·925	
	(0·500–0·736)	(0·699–1·039)	(0·755–1·133)	
p†	<0·0001	0·115	0·453	

*p=0·003 *vs* placebo. †vs combination treatment. ‡p=0·0003 *vs* placebo. §p=0·0001 *vs* placebo.

Table 3: **Effect of 52 weeks' treatment on exacerbation rate**

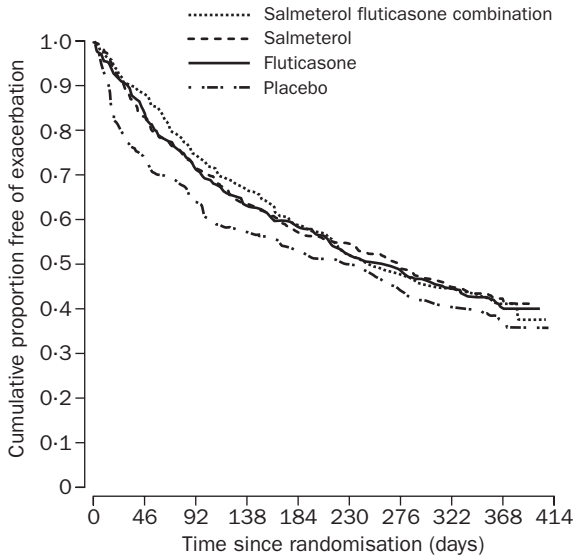

Figure 3: **Cumulative risk of acute exacerbations**

combination compared with placebo, as against a 10% reduction in patients who had a baseline FEV_1 that was greater than 50% of that predicted. Acute episodes of symptom exacerbation that required oral corticosteroids were reduced by 39% in the combination group (p<0·0001), 29% in the salmeterol group (p=0·0003), and 34% in the fluticasone group (p=0·0001), compared with placebo. There were no significant differences between active treatments with respect to their effect on the rate of episodes of symptom exacerbation (table 3), time to first exacerbation, or number of hospital admissions. Figure 3 shows the cumulative risk of acute exacerbations.

Combination treatment significantly reduced breathlessness and the use of relief medication compared with placebo, salmeterol, and fluticasone (table 4). Median number of days without relief medication was for placebo 0% (range 0–100%), salmeterol 3% (0–100%), fluticasone 2% (0–100%), and combination 14% (0–100%) (p<0·0001 *vs* placebo, p=0·004 *vs* salmeterol, p=0·0003 *vs* fluticasone). The number of night-time awakenings fell significantly in the combination group, compared with placebo and salmeterol, but not with fluticasone (table 4). Cough only improved significantly in the combination group (table 4).

Only the combination group showed a clinically significant improvement in health status questionnaire score by week 52. The raw mean changes in health status total score were –4·3 (SD 10·8) by week 8 and –4·5 (12·9) at week 52 (figure 2). The change in SGRQ score in the combination group over 52 weeks at the end of the study was significantly greater than that in both the placebo and fluticasone groups (table 4).

All treatments were well tolerated, and there were no differences between groups in the number of patients reporting an adverse event during treatment (78–81% across all groups), apart from an increased frequency of oropharyngeal candidosis (placebo 2%, salmeterol 2%, fluticasone 7%, combination 8%). Table 5 shows adverse events that were judged to be treatment-related. Most patients (≥96%) had serum cortisol values that were within the reference range, or that did not change significantly from baseline after 24 or 52 weeks of treatment. 13 (4%) and 11 (4%) patients in the placebo and salmeterol/fluticasone groups, respectively, had a change from within to below the reference range, compared with 17 (5%) and 19 (6%) in the salmeterol and fluticasone groups, respectively. None of these changes was clinically important. After 52 weeks' treatment, mean serum cortisol concentrations rose by 4% in placebo and 6% in the salmeterol group, whereas they fell by 1% with fluticasone and by 3% with the combination treatments. The differences between fluticasone and placebo were significant at weeks 24 (p=0·035) and 52 (p=0·007), and between combination and placebo at week 24 (p=0·020). None of the changes were associated with any clinical effects or signs of hypoadrenalism.

We noted skin bruises in a maximum of 22 (6%) of patients in the placebo group, 20 (6%) in salmeterol, 26 (7%) in fluticasone, and 29 (8%) in the combination group at any visit. We did not detect any changes on echocardiograms that could be attributed to treatment.

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
SGRQ total score				
Adjusted mean	46·3 (0·5)	45·2 (0·4)	45·5 (0·4)	44·1 (0·5)
Treatment difference* (95% CI)	–2·2 (–3·3 to –1·0)	–1·1 (–2·2 to 0·1)	–1·4 (–2·5 to –0·2)	
p*	0·0003	0·071	0·021	
Symptom scores				
Cough	1·44 (0·03)	1·36 (0·03)	1·38 (0·03)	1·35 (0·03)
p*	0·018	0·639	0·340	
Breathlessness	1·66 (0·03)	1·59 (0·03)	1·58 (0·03)	1·47 (0·03)
p*	0·0001	0·006	0·010	
Sputum production	1·34 (0·03)	1·30 (0·03)	1·33 (0·03)	1·29 (0·03)
p*	0·196	0·687	0·339	
Sputum colour	1·36 (0·03)	1·35 (0·03)	1·37 (0·03)	1·32 (0·03)
p*	0·373	0·494	0·250	
Median (range) use of relief medications (per day)	2 (0–32)	2 (0–14)†	2 (0–11)‡	1 (0–10)
p*	<0·0001	0·0001	0·0003	
Mean number awakenings per week	3·01 (0·21)	2·94 (0·21)	2·45 (0·21)§	2·31 (0·21)
p*	0·006	0·011	0·591	

SGRQ=St George's Respiratory Questionnaire. Data are mean (SE), unless otherwise indicated. A negative value represents an improvement in health status. **vs* combination; †p=0·028 *vs* placebo; ‡p=0·010 *vs* placebo; §p=0·024 *vs* placebo.

Table 4: **Effect of 52 weeks' treatment on health status and symptoms**

	Placebo (n=361)	Salmeterol (n=372)	Fluticasone (n=374)	Combination (n=358)
Any treatment-related event	49 (14%)	46 (12%)	70 (19%)	58 (16%)
Oropharyngeal candidosis	5 (1%)	5 (1%)	23 (6%)	22 (6%)
Candidosis in unspecified site	0	2 (<1%)	8 (2%)	1 (<1%)
Oral inflammation or nausea and vomiting	8 (2%)	3 (<1%)	3 (<1%)	4 (1%)
COPD exacerbation	19 (5%)	8 (2%)	10 (3%)	9 (3%)
Cough, breathing disorder, or lower respiratory infection	6 (2%)	7 (2%)	6 (2%)	3 (<1%)
Throat infection or hoarseness	8 (2%)	8 (2%)	16 (4%)	15 (4%)
Headaches, tremor, or vertigo	4 (1%)	10 (3%)	2 (<1%)	4 (1%)

Table 5: **Treatment-related adverse events**

Discussion

Ideally, any new treatment for COPD should improve one or more of the endpoints outlined in the GOLD (Global Initiative for Chronic Obstructive Lung Disease) management protocol[25]—symptoms, health status, and frequency of exacerbation. These effects should be sustained and better than those of existing treatments. Many treatment trials in COPD have only lasted 3–6 months,[18,26] or if longer, they have compared only one active treatment with placebo. Our trial has compared commonly prescribed agents from different therapeutic classes for a sufficient time to see changes in a range of clinically relevant outcomes. Our results confirm that active treatment is better than placebo. A combination of different types of treatment produces benefits across a range of endpoints that translate into a clinically noticeable benefit for patients, as indicated by the health status data.

Consistent changes were seen in the pretreatment FEV_1, suggesting a drug effect before the first dose taken in the day. Both salmeterol and fluticasone produced small but significant improvements in FEV_1 in keeping with previous findings,[7,17,18] but combination treatment was significantly more efficacious than either placebo or the individual components. Postbronchodilator FEV_1 improved after fluticasone, as also noted by investigators in the ISOLDE study.[17] Patients in the combination group had the lowest bronchodilator responsiveness (ie, the change between pretreatment and post-treatment FEV_1), suggesting that part of the pretreatment effect in patients in the combination group was caused by the bronchodilatory effects of salmeterol taken 12 h previously. However, despite this effect, patients in the combination group had a significantly higher postbronchodilator FEV_1 than with either agent alone. Data for FVC showed much the same trend as that seen for FEV_1, but are more relevant to improved exercise performance in COPD. Finally, the multiple daily readings of peak expiratory flow showed a sustained improvement throughout the year, which was significantly greater in the combination group, and evident within 1 week of randomisation. These early changes in lung function could provide a useful guide to subsequent patient benefit, but this indicator has not yet been formally tested.

Improved lung function was associated with reductions in the number and type of symptoms recorded in the daily diary cards. Although scores for cough and sputum did not change greatly, breathlessness was reduced by both salmeterol and fluticasone but significantly more so with combination treatment. Much the same pattern was seen with rescue treatment, and in the amount of sleep disruption. These data represent daily recordings for 1 year in every patient, and confirm the sustained nature of the clinical benefits. Health status measurement provides an integrated assessment of the effect of COPD on patients' health, and has been widely validated.[27,28] A 4-unit reduction in total St George's respiratory questionnaire score is associated with both subjective and objective improvement, such as the ability to walk further and less perceived breathlessness before and after exercise.[12,29,30] This improvement was achieved by patients in the combination treatment group after 12 months, but not by those who received single-drug treatment or placebo. The speed of change in health status was less striking than with lung-function tests but was still evident by 8 weeks, in keeping with other data about long-acting β2 agonists.[9] The lower than expected frequency of acute episodes of symptom exacerbation in patients who received placebo might explain some of the health status improvement.

All active treatments were associated with a lower rate of exacerbations than was placebo. Despite differences in definition, we noted a self-reported exacerbation rate that was similar to that in other trials—ie, 1·3 per year with placebo.[4,17] Combined treatment reduced the total exacerbation rate by 25% and exacerbations that required oral corticosteroids by 39%, which were all significant changes compared with placebo. Although these reductions were not statistically significant when compared with monotherapy, there was a trend in favour of the combination group which became more pronounced with increasing COPD severity. Despite our selection criteria, we saw substantially fewer exacerbations than expected (46% of patients did not have such an incident), which significantly reduced the power of the study to show a difference. The low rate of acute episodes might be attributable to regression to the mean in exacerbation number or an effect of improved care associated with clinical trials, but suggests that a study of longer duration and with a larger number of participants would be needed to show a difference. All active therapies were well tolerated, and there was no evidence of important cardiac side-effects with salmeterol, or any unanticipated problems with fluticasone. There were minor changes in cortisol secretion with fluticasone monotherapy and with combination treatment, which did not differ from those previously reported.[17,18]

The reasons why combination treatment proved to be most effective remain speculative. Results from research in asthma suggest that long-acting β_2 adrenoceptor agonists can enhance the anti-inflammatory effect of corticosteroids.[31] Although the absolute changes in lung function induced by combination treatment in our study were modest, they did happen rapidly, and were noticeable after 2 weeks. Such improvements could be sufficient to allow improvement in exercise tolerance and reduce the perceived severity of an exacerbation, and hence the number of episodes reported. Both factors are important determinants of health status.[17,32] The additional effect of an inhaled corticosteroid on

postbronchodilator FEV_1 has been noted before.[17] β receptor numbers can be upregulated with corticosteroids, and the combination is more effective in reducing induced interleukin 8 release from airway smooth muscle.[33] Whether this mechanism is important in COPD remains to be established

Contributors

P Calverley, R Pauwels, J Vestbo, A Gulsvik, P Jones, and N Pride, designed the study, reviewed the analysed data, and wrote the manuscript. C Madden designed the study, interpreted results, and helped to write the manuscript. J A Anderson analysed data, interpreted results, and helped to write the manuscript.

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Conflict of interest

P Calverley, R Pauwels, J Vestbo, A Gulsvik, P Jones, and N Pride have been consultants for, and received research grants from, GlaxoSmithKline. J Vestbo is married to an employee of GlaxoSmithKline. J Anderson and C Madden are employees of GlaxoSmithKline and hold shares in the company.

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Uses of error

The right word

G Burnham

Error is a grim idea, with connotations of bias, misjudgment, and increasingly, of liability. Yet the inadvertent and the fortuitous have given medicine a number of its great successes. Many of the errors noted in this *Lancet* series have centred on lessons practitioners have learnt from clinical misjudgments. Fewer have come from public health or population-based endeavours. As with clinical medicine, these chance occurrences are both prevalent and underacknowledged.

When ivermectin was first being tested for effectiveness in onchocerciasis we set out to measure its adverse reactions when given as mass treatment. The three-year study was conducted in an endemic area of Malawi using a double blind, placebo-controlled design. For these multi-site trials, the World Health Organization had set explicit criteria for exclusion of subjects from the study. Because of the potential for ivermectin to cross the blood-brain barrier in mice, it was thought that persons with a history of epileptic fits should not receive treatment. This was an important consideration for us since epilepsy was quite common in this part of Malawi, and our hospital ran a heavily patronised outreach service for its treatment.

Instructions for potential ivermectin recipients were translated into the vernacular, back translated, and then pilot tested in a nearby non-study site for comprehension. Changes were made as necessary to instructions. The importance of epilepsy as a reason for not participating was specifically noted in the verbal instructions to potential participants.

After the first round of treatment it became evident that almost no one had been excluded from treatment because of a history of epilepsy. Pursuing this it was discovered that the specific word used for epilepsy was not recognised in the study villages even though the language was the same as in the pilot area where the instructions had been pre-tested. In a hurried follow-up we identified some 80 persons with epilepsy who had been unintentionally treated with ivermectin. Further investigations in this cohort with a history of epilepsy revealed that no fits had followed treatment. The cohort was then followed through the two subsequent annual treatment rounds during which there was no association between receiving treatment and having fits. On the basis of these Malawi findings, a history of epilepsy was dropped as a reason for excluding treatment in the subsequent ivermectin mass-treatment programmes for onchocerciasis. The outcome from this error of words has been that tens of thousands of epileptics living in 37 countries where onchocerciasis is endemic have been treated regularly as a prevention against this physically disabling and potentially blinding disease. This is another reminder that a study may yield important findings aside from the answering of the original research questions.

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