Research Review
EDUCATIONAL SERIES

Treating Chronic Obstructive Pulmonary Disease (COPD)

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Introduction
The following publication is intended as an educational resource for health professionals. It presents a short background on COPD in New Zealand and a review of selected peer reviewed studies featuring medicines used to treat the condition. It is intended to help readers stay informed of developments and advancing clinical practice in the areas covered.

According to the WHO, COPD will be the third leading cause of death worldwide by 2020[1], largely due to increased smoking rates worldwide over the last half-century. Its significance in New Zealand continues to grow with over 1500 deaths attributed to COPD in 2002[2].

Defining COPD
COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease[3] as:

> *"A disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases".*

There are many other definitions. A simpler explanation is found in the Burden of COPD in New Zealand[4]:

> *"...a chronic respiratory condition presenting as slowly progressive breathlessness, often associated with cough and sputum production. It includes both chronic bronchitis and emphysema in variable proportions in any one patient".*

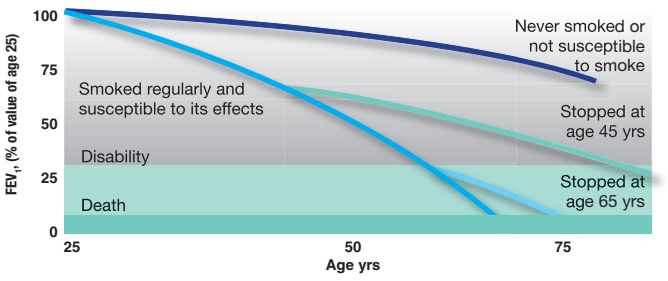
The term COPD encompasses three distinct clinical and pathological conditions, with individual patients having features of one, two or all three of these present:

- **Chronic bronchitis** – chronic cough and sputum production for at least 3 months of 2 consecutive years
- **Emphysema** – abnormal dilatation of the terminal air spaces with wall destruction and loss of lung elasticity
- **Asthma** – airways inflammation with widespread obstruction, which is reversible either spontaneously or with treatment, and which can become irreversible

Once the diagnosis has been established, it is useful to classify patients according to their severity. Patients who have smoked and have chronic cough or sputum production but normal lung function tests are at risk of COPD. When the FEV1/FVC ratio falls below 70%, then COPD can be diagnosed and classified as:

- **Mild** – FEV1 80% of predicted or more
- **Moderate** – FEV1 30-79% predicted
- **Severe** – FEV1 less than 30% predicted, or less than 50% predicted if the patient has respiratory failure or clinical signs of right heart failure[3]

The Burden of COPD
In order to understand the burden of COPD and how this is changing, we need to appreciate the causes. 90% of cases of COPD are due to smoking, with the inhaled smoke causing permanent damage to the mucus glands and destruction of alveolar walls. The



decline in lung function is accelerated by smoking[5].

Other risk factors include alpha-1 antitrypsin deficiency, occupational exposures to dust and pre-existing bronchial hyper-responsiveness.

The WHO estimated in 1990 that the prevalence of COPD worldwide was around 0.9% in males and 0.7% in females[1]. However these estimates cover all age ranges and so the prevalence is markedly higher in older populations. COPD is currently the 4th leading cause of death worldwide and increases in prevalence are expected, given the widespread uptake of smoking in developing countries. In terms of disability-adjusted life years, COPD ranks at No.12 relative to other conditions. An estimated 3 million people die of COPD each year[6].

In New Zealand, WHO data suggests that around 15% of adults > 45 years old have COPD. That would mean there are around 200,000 patients in New Zealand, with only around one fifth of these having the diagnosis confirmed by a doctor. The prevalence in Maori is around double that of non-Maori[4].

Identifying patients with COPD

As highlighted above, up to 80% of patients with COPD do not have a doctor diagnosis of their condition. In basic terms, patients who have shortness of breath, chronic cough or sputum productions may have COPD, especially if they are 40 years or older and have a history of current or former smoking.

To confirm the diagnosis, spirometry should be performed to determine the presence and severity of any airway obstruction. COPD is formally diagnosed when the post-bronchodilator FEV1/FVC ratio is <0.7 in the absence of an alternative respiratory disorder. Ideally spirometry should include the following parameters:

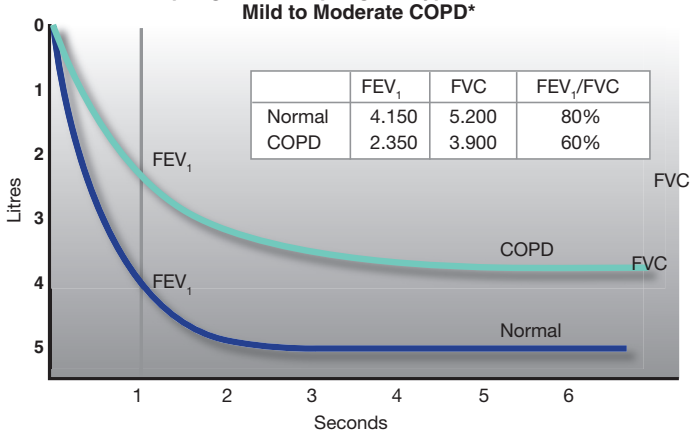
1. **Forced Vital Capacity (FVC)** – the volume of air that can be exhaled in a forced manoevre after a maximal inhalation
2. **Forced Expiratory Volume in 1 second (FEV1)** – the volume of expired air in the first second of this manoevre
3. **FEV1/FVC ratio** – this is then easily calculated and most modern spirometers will undertake this calculation automatically

Practice Tip – Doing Spirometry

In practical terms, the patient can be instructed to undertake the spirometry manoevre as follows: *"I want you to breathe in as deeply as you can, then blow out as hard as you can and for as long as you can".* The patient should be encouraged to *"keep going, keep going"* during the manoevre and should ideally perform 3 manoevres. However, with elderly patients or those with advanced disease, it may not be possible to obtain 3 good spirometry manoevres and common sense should be adhered to and the testing stopped if the patient is clearly struggling after 1-2 blows.

If spirometry is abnormal, then you should repeat 30 minutes after administering 400mcg of salbutamol, in order to determine the post-bronchodilator FEV1/FVC ratio.

Normal Spirogram and Spirogram Typical of Patients with Mild to Moderate COPD*



	FEV_1	FVC	FEV_1/FVC
Normal	4.150	5.200	80%
COPD	2.350	3.900	60%

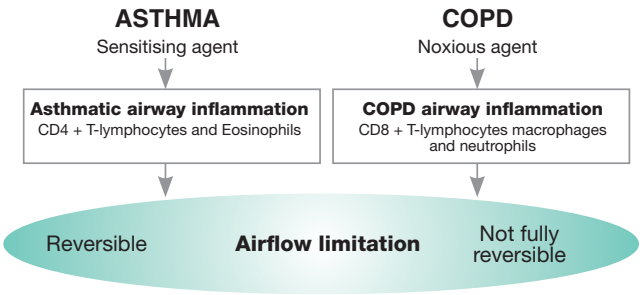
***Postbronchodilator FEV1 is recommended for the diagnosis and assessment of severity of COPD**

As discussed earlier, a FEV1/FVC ratio <70% is characteristic of airways obstruction and the severity of the obstruction is given by the FEV1 predicted.

A major difficulty, particularly in primary care, can be differentiating COPD from chronic asthma, as there is no gold standard definitive test for this. Many patients with asthma meet the diagnostic criteria for COPD, reflecting patients with asthma whose airways obstruction is not fully reversible. Pathologically, one of the main differences is that the inflammation in asthma is characterised by the presence of eosinophils and in COPD inflammation is characterised by the presence of neutrophils. However, in practical terms, the following rules of thumb are helpful in making the diagnosis:

1. Adult-onset asthma in current or former smokers is unusual and these patients will almost certainly have COPD
2. Asthma is usually reversible (an increase in FEV1 of 12% or more after inhalation of 400mcg of salbutamol) whereas COPD is largely irreversible (an increase in FEV1 of <5% or more after inhalation of 400mcg of salbutamol)
3. Asthma symptoms vary considerably, even on a day-to-day basis, whereas COPD is a slowly progressive disease
4. Patients with asthma often have a history of other allergic disorders, such as allergic rhinitis or eczema
5. Patients with asthma often have a history of asthma in their family
6. The response to inhaled corticosteroid inhalers is usually large and even dramatic in patients with asthma, whereas in COPD improvements are modest at best

Asthma and COPD



Although the diagnosis can be difficult notwithstanding the above pointers, the management of COPD and chronic asthma overlap to a large degree and so a less than perfect diagnosis may not affect management or outcomes.

Treating patients with COPD

This section provides a brief overview of the management of patients with COPD and will focus on the main areas of concern for primary care, namely, the effectiveness of maintenance inhaler therapy.

Non-pharmacological treatment is an important part of management and consists of the following:

- Smoking cessation – *Key research findings discussed later*[7]
- Pulmonary rehabilitation programs - *Key research findings discussed later*[8]
- Education – This is often neglected and can help patients cope with the illness, stop smoking and in particular manage exacerbations
- Oxygen – administration of oxygen for >15 hours a day has been shown to increase survival in patients with chronic respiratory failure[9]. The goal is to increase baseline PaO2 in patients with severe COPD who have PaO2 < 7.3 kPa, or PaO2 < 8.0 kPa if the patient also has right-sided heart failure
- Surgical options – bullectomy, lung volume reduction surgery or lung transplantation may be options for carefully selected patients who are also under specialist care

Pharmacological treatments are best discussed in terms of the management of acute exacerbations and long-term maintenance therapy.

Acute exacerbations of COPD are ideally managed in the community, with oral antibiotics, steroid tablets and inhaled bronchodilators. Hospital admission may be required if the patient has severe disease, develops new clinical signs such as cyanosis, does not respond to treatment, has significant co-morbidities or is elderly with insufficient home support.

Long-term maintenance therapy of patients with stable but slowly progressive COPD has long been a concern to primary care practitioners and this may be due to the apparent small and often inconsistent improvements seen when various inhalers are prescribed. Two of the landmark studies, ISOLDE and TORCH, are discussed later[10,11].

(i) **As needed inhaled bronchodilators** - These can be prescribed as needed for relief of symptoms or regularly to prevent or reduce symptoms. Short-acting bronchodilators include beta-2-agonists such as salbutamol, anticholinergics such as ipratropium bromide and the combined inhaler containing both of these medications.

(ii) **Inhaled corticosteroids (ICS)** - Regular treatment with ICS should be given to patients who have a positive response to a trial period, either in terms of an improvement in symptoms or an improvement in lung function as assessed by spirometry. ICS do not reduce the long-term steady decline in lung function to any significant degree, but this does not preclude their use for the above reasons[10]. In addition, the GOLD recommendation is that ICS should be used in patients with an FEV1 < 50% predicted who have repeated exacerbations[3]. Despite their widespread use, neither the dose-response relationship nor the long-term side effect profile are well understood. 6-12 weeks is the recommended time for a trial of ICS. Previously, it was considered good practice to have the trial period with oral steroid rather than inhaled steroid, but recent evidence suggests this is not a good predictive indicator[9].

(iii) **Long-acting bronchodilator drugs** - The long-acting beta-agonist drug salmeterol has been shown to improve health status significantly at doses of 50mcg twice a day and the new long-acting anticholinergic drug tiotropium has produced some very positive results. As beta-agonist and anticholinergic medications have different mechanisms of action, they can be co-prescribed if you consider the patient may benefit from taking both[12].

(iv) **Vaccinations** - GPs should have systems in place to ensure patients with COPD are vaccinated against influenza each year. Consideration should also be given to using the pneumococcal vaccine.

(v) **Oral bronchodilators** - Both aminophylline and theophylline can have bronchodilator actions for up to 24 hours. It is reasonable to try these medications in some patients, but there is a large variability in response in terms of efficacy, and more importantly, dose-dependent side effects are common. The GOLD guidelines state that inhaled therapy is preferred[3].

(vi) **The future** - There are many exciting drugs in the early stages of development for patients with COPD, with novel mechanisms of actions, offering hope to sufferers. One development that is highly likely to happen will be the development of triple therapy inhalers, containing an ICS, long-acting beta-agonist and long-acting anticholinergic medication. It is hoped that there may be small but important benefits from all three components and possibly some synergistic effects.

Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study.

Authors: Burge PS et al.

Summary: Patients with chronic obstructive pulmonary disease were found to benefit from treatment with inhaled fluticasone propionate according to the findings from the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study. Patients, aged 40-75, with moderate to severe COPD were withdrawn from their usual inhaled or oral corticosteroids and started an 8-week run-in period, during which time baseline lung function was assessed. For the final two weeks of the run-in patients received oral prednisolone 0.6 mg/kg/day. 751 patients were subsequently randomised to receive either 500mcg inhaled FP twice daily or a matching placebo for 3 years in this double-blind, placebo-controlled study. Both groups of patients experienced a drop in FEV1 during the initial withdrawal of their usual medication, followed by an improvement during prednisolone treatment. FEV1 then continued to decline during the study, and, although the rate of decline was more marked initially in the placebo group the rate of decline was not statistically different between the groups throughout the study. Post-bronchodilator FEV1 was consistently higher in the FP group than the placebo group and patients receiving FP had a lower median annual rate of exacerbations compared to those taking placebo (0.99 vs. 1.32). Health status, as assessed by the St. George's respiratory questionnaire, declined at approximately the same rate in both groups, although the respiratory questionnaire revealed a faster rate of decline in the placebo group. Adverse events were similar between the groups with typical corticosteroid effects being observed in the FP group. Cortisol levels below the normal range were seen in less than 5% of patient receiving FP (at any one time). 19% of patients treated with FP withdrew during the study because of non-malignant respiratory conditions compared to 25% of those receiving placebo. The authors conclude that inhaled FP, at this dose, is an appropriate treatment for COPD in this patient population.

Comment: This landmark study provided firm evidence of the efficacy of inhaled corticosteroids in reducing the frequency of severe exacerbations of COPD in patients with moderate to severe disease. The reduction in exacerbations was associated with an improved health status. The clinical improvement demonstrated in the study is likely to be conservative in terms of that which might be achieved in clinical practice due to the enrolment of COPD subjects with <10% improvement in FEV1 after bronchodilator. In clinical practice, many patients with COPD have greater degrees of reversibility and it is likely

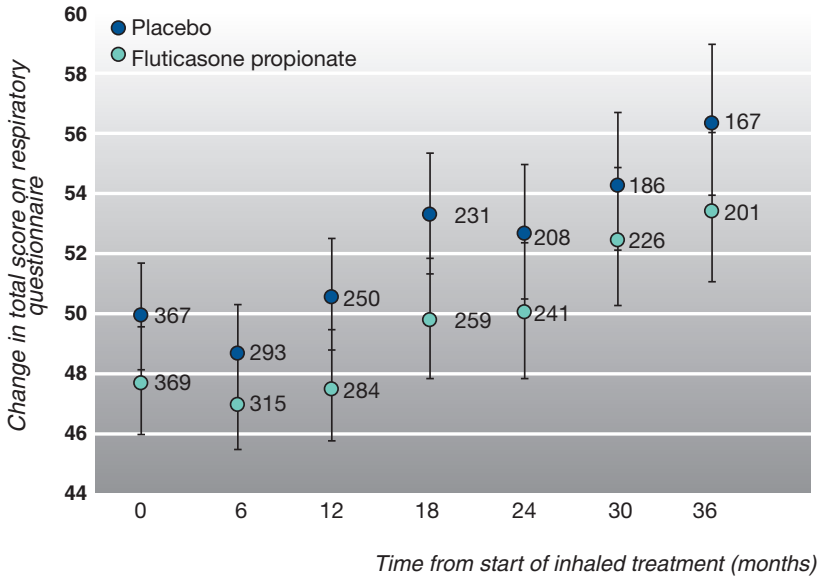
that they may well achieve a greater benefit from inhaled corticosteroid therapy, due to the greater "asthmatic component" to their airflow obstruction.

This study was also able to investigate the established clinical practice at the time, that the response of COPD patients to a trial of oral corticosteroids could be used to identify "responders" who would be suitable for long term inhaled corticosteroid therapy. However, the study showed that patients with COPD cannot be separated into discrete groups of corticosteroid "responders" and "non-responders". More importantly, the response to a course of oral steroids was an unreliable predictor of the benefit from inhaled corticosteroids in individual patients. As a result, this approach can no longer be recommended for use in the management of patients with COPD.

Another intriguing finding from the study was that current smoking was the factor most strongly associated with response to prednisolone, with ex-smokers having double the improvement in FEV1 than current smokers. This finding has subsequently been confirmed in clinical trials which have shown that the response to inhaled corticosteroids and oral steroids in both asthma and COPD is markedly reduced in smokers. This is another important reason why smokers with asthma or COPD should be encouraged to stop smoking and raises the issue of whether higher doses of inhaled steroids should be used in the long term treatment of these conditions, and/or higher doses of oral steroids during exacerbations.

Effect of treatment on decline in health indicated by increasing total scores on respiratory questionnaire (means (95% confidence intervals) calculated from analyses of covariance). Numbers at each assessment indicate number of patients for whom measurements of health status were available at that visit. Direct comparisons of respiratory questionnaire scores at each time point are not possible because fewer patients remained in the study as it progressed.

Reference: Thorax 2003; 58: 654-8



Respiratory rehabilitation in chronic obstructive pulmonary disease: predictors of non-adherence.

Authors: Young P et al

Summary: In this New Zealand study published in 1999 the investigators examined the factors that influence a patient's ability to adhere to a respiratory rehabilitation programme. Patients, aged at least 50, with a diagnosis of moderate to severe COPD who attended a COPD clinic, were asked to complete a questionnaire. The questionnaire encompassed socio-economic factors (e.g. employment and accommodation arrangements), respiratory and COPD status, quality of life, depression and anxiety and the level of support available to the patient. Patients were then invited to take part in a four-week rehabilitation programme. At the end of the study period patients were classified as either adherent, if they had completed the programme, or non-adherent, if they had either declined to take part or had withdrawn during the study. 55 patients were classified as adherent and 36 as non-adherent. The study showed that patients who were non-adherent generally had a lower socio-economic status, were more likely to be living in rented accommodation, were more likely to be divorced, widowed or living alone, were more likely to be current smokers and had a lower level of support. COPD status, medication and previous health complications were similar between the groups, but those in the non-adherent group were less likely to be taking high dose inhaled corticosteroids. Psychological disturbances were slightly higher in the non-adherent group, although this was not statistically significant. The authors suggested that the presence of at least one of these factors should be predictive of a patient's ability to successfully participate in a COPD rehabilitation programme.

Comment: This study has shown that a substantial proportion of patients refused to participate or failed to complete a hospital-based COPD rehabilitation programme. Non-adherent patients are likely to be socially isolated and lack COPD-specific social support. These findings are important when the potential benefits of pulmonary rehabilitation are considered. They suggest that the establishment of GP-based pulmonary rehab programmes may be a worthy alternative, as they are likely to be easier for isolated elderly patients to access. They could be combined with cardiac and neurology (stroke) rehab, in which the programmes have similar principles and practices. With the gradual cut-back of hospital outpatient-based programmes in New Zealand, a community GP-based multidisciplinary rehab programme can be recommended as a worthwhile initiative to consider.

Reference: Eur Respir J 1999; 13: 855-9.

Odds ratio and 95% confidence intervals for predicting adherence with a respiratory rehabilitation programme for chronic obstructive pulmonary disease (COPD)

Variable	Odds ratio	95% confidence interval
Married*	7.2	2.8-18.5
Current smoker⁺	0.3	0.1-0.9
Own house#	7.7	2.0-29.7
Lack of COPD social support‡	0.1	0.0-0.3

*: Married=0, not married (divorced or widowed)=1; ⁺: current smoker=0, exsmoker=1; #:own house=0, rented or other=1; ‡:lack of, or inadequate COPD-related social support=0, satisfactory level of COPD-related social support=1.

Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library

Authors: Lancaster T et al.

Summary: The Cochrane Tobacco Addiction Review group compiled a series of reviews for the Cochrane Library, that examined the effectiveness of a variety of different smoking cessation techniques. Their data were taken from high quality, controlled clinical studies of at least 6 months' duration and are used to provide guidance to the health sector and the public on the most effective methods of quitting smoking. This 2000 publication provides an oversight of the findings from the reviews which can be summarised as follows: Advice from a GP or nurse is effective in improving the quit rate, with more intensive or personalised advice being more effective. Individual counselling or group therapy is also beneficial but self-help programmes have only limited success. Nicotine replacement therapy has the potential to double the quit rate, and no marked difference was found between the different types (e.g. gum, patches, inhaler). Bupropion is effective at reducing smoking rates but anxiolytics are not. The review also examined other therapeutic classes and alternative approaches such as acupuncture and hypnotherapy with no clear conclusions being drawn. The authors conclude that there are a number of effective strategies for assisting

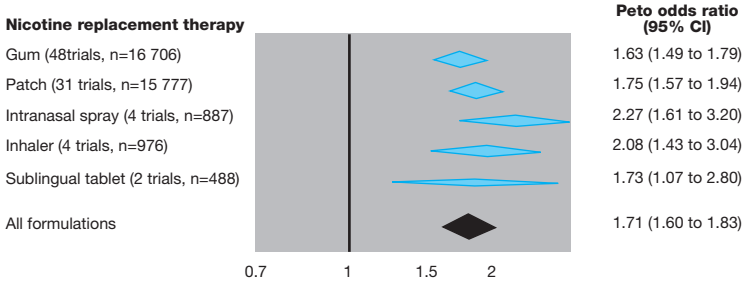
Comment: The most important finding of this systematic review is the effectiveness of simple brief advice by doctors and nurses to stop smoking. This represents the most cost-effective method to help people stop smoking and ideally should represent a component of every "medical/ consultation" with a smoker. The benefits of this approach can be enhanced by more intensive advice such as with individual counselling.

Nicotine replacement therapy improves the quit rate from whatever baseline is set by other interventions. The choice of nicotine product depends on both patient and doctor preference, with more than one product often used in combination. A number of practical tips came out of the review – patches need only be worn for 16 hours per day (i.e. can be taken off at night), 8 weeks is as effective as longer courses, and abrupt withdrawal is as good as tapered withdrawal.

There is also good evidence that bupropion and to a lesser extent, nortriptyline, is effective in helping smoker quit. A recent double blind placebo-controlled trial of bupropion in heavy smokers in a Maori community has confirmed the efficacy of this approach. The effect of alternative therapies has not been proven, although there is likely to be a substantial placebo effect which means that their use can be supported in patients who are keen to give them a try.

Reference: BMJ 2000; 321: 355-8

Meta-analysis of the effect of nicotine replacement therapy on smoking cessation



The TORCH (Towards a Revolution in COPD) study: salmeterol and fluticasone proprionate and survival in COPD

Authors: Calverley PMA et al

Summary: Combination therapy with salmeterol and fluticasone propionate (FP) improved survival over a 3-year period in patients with COPD reducing the risk of dying by 17.5% compared with placebo (p=0.052). The randomised, double-blind, placebo-controlled study compared the effects of salmeterol 50µg and FP 500µg given twice daily in combination or alone for 3 years in over 6000 patients with COPD (<60%predicted FEV1, 44% predicted post-bronchodilator FEV1, 43% current smokers). The primary analysis at 156 weeks was log-rank of time to all-cause mortality. This was also monitored through interim analysis conducted by an independent monitoring board. Given alone, salmeterol and FP had no significant effect on survival compared with placebo. The authors commented that the salmeterol/FP combination is the first intervention since smoking cessation and oxygen therapy to prolong life in COPD.

Log-rank of time to all-cause mortality at 156 weeks, adjusted for 2 interim analyses.

	Risk of dying at any time during the 3 yrs
Salmeterol / fluticasone combination	12.6%
Placebo	15.2%

Comment: The TORCH study findings, reported that salmeterol/ fluticasone combination therapy (but not the individual components) improves survival in COPD over 3 years. This is the first study to show an improvement in mortality in patients from COPD from a medication.

Despite being a huge study, and possibly the largest COPD study ever, the p value for the primary end-point was an agonising 0.052 and it could be that the enrolment of a few more patients could have produced a statistically significant result.

As well as the data on mortality, a wealth of data relating to other important outcome measures has also been published. The primary outcome measure was mortality, but important secondary outcome measures included health status, as assessed by the St George's Respiratory Questionnaire (SGRQ); number of moderate/severe exacerbations and FEV1 30 minutes after taking bronchodilator. Salmeterol/fluticasone combination therapy was statisitically and clinically superior to placebo and the individual componants with respect to all of these clinically relevant outcomes.

Treatment difference

	SFC vs PL (95% CI)	SFC vs SAL (95% CI)	SFC vs FP (95% CI)
SGRQ Total score (units)	-3.1 (-4.1, -2.1) p<0.001	-2.2(-3.1,-1.2) p<0.001	-1.2(-2.1,-0.2) p=0.017
Moderate/severe * exacerbations rate ratio	0.75 (0.69, 0.81) p<0.001	0.88 (0.81, 0.95) p=0.002	0.91 (0.84, 0.99) p=0.024
Postbronchodilator FEV_1 (mL)	92 (75,108) p<0.001	50 (34,67) p<0.001	44 (28,61) p<0.001

*moderate: antibiotics and/or systemic corticosteroids; severe: hospitalisation.

Safety is of course as important as efficacy when considering prescribing long-term medications to COPD patients. Data presented at the 2006 ERS conference showed that investigator reported adverse events occurred in a similar frequency in all 4 groups. Safety measures assessed included HPA axis, pneumonias, fractures and cardiac adverse events. The authors concluded that, when considered alongside the clinical benefits, the salmeterol/fluticasone combination had a beneficial long-term risk/benefit ratio when compared to placebo.

The implications of this landmark study will be discussed in the medical literature for years to come.

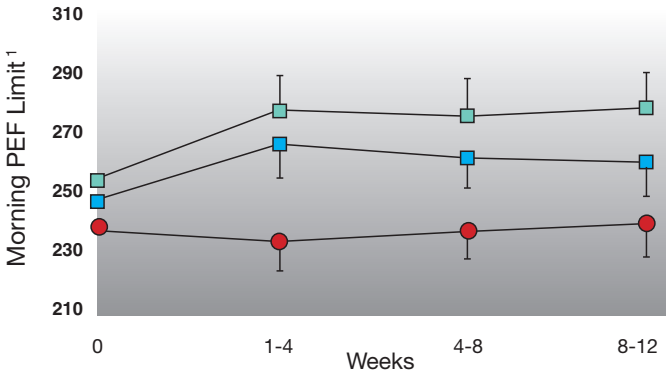
Reference: N Engl J Med 2007; 356: 775-89

Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium

Authors: van Noord JA et al

Summary: Salmeterol and salmeterol in combination with ipratropium bromide were both found to be effective in the management of severe, stable COPD in this multi-centre, placebo-controlled, randomised clinical study performed in the Netherlands. 144 patients aged 57-71 with an FEV1 of 33-55% predicted were randomised to receive either 50mcg salmeterol twice daily, 50mcg salmeterol twice daily in combination with 40mcg ipratropium four times daily or placebo for 12 weeks. After the first dose FEV1 increased by approximately 7% in the salmeterol group and 11% in the salmeterol + ipratropium group with peak increases being seen 2 hours after dosing. Increases of 2% and 3% in FEV1 were still apparent 12 hours after dosing for the monotherapy vs. combination treatment. Patients were then monitored at 4 weekly intervals for the remainder of the study. Both active treatments resulted in a decrease in day and night time symptom scores and use of rescue medication compared to placebo, and an increase in FEV1, FVC, specific airways conductance and morning peak flow during the 12 week study period. Treatment effects were consistently greater following salmeterol + ipratropium than salmeterol alone, with the difference between the active treatment groups reaching statistical significance on some occasions. The incidence of adverse events was similar between the three groups but the rate of COPD exacerbation was higher in the placebo group (36%) than in either of the active treatment groups (23% for salmeterol and 13% for the combination). The authors conclude that both treatment regimens are effective in patients with severe stable COPD with slightly greater benefit being achieved with the combination therapy.

Comment: This was an important study. The study was well designed and showed clearly that the addition of a medication with a different mechanism of action produced additional benefits. These benefits were seen in a wide range of outcome measures, including lung function, reduction of subjective symptoms, use of rescue medication and, importantly, exacerbations.



Peak expiratory flow (PEF) in the morning over 4 week periods before and during treatment with salmeterol (■), salmeterol plus ipratropium (■) and placebo (●). Data are presented as mean +/-SEM

The implications from this study are likely to impact on the treatment of COPD in the future. As improvements from COPD medications tend to be modest, it is useful to know that giving several medications, each with small but additive benefits, may lead to an overall clinical benefit that can make an important difference to the quality of life of patients with COPD.

It may not be too long until we have products available that deliver 3 or more medications from a single inhaler. These medications are likely to include new long-acting inhaled corticosteroids, long-acting beta-agonists, long-acting anticholinergics and new classes of medications that are currently undergoing clinical trials. Trials are underway for once daily versions of many of these medications and so the COPD patient of the future may obtain good benefits from a single daily puff of an inhaler.

Reference: Eur Respir J 2000; 15: 878-885

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