# COPD and the inhaled corticosteroid debate

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*The use of inhaled corticosteroids to manage chronic obstructive pulmonary disease (COPD) is controversial. While there is no evidence that they slow the progression of this condition, recent studies suggest that high dose inhaled corticosteroids may decrease exacerbations of COPD and improve quality of life.*

Chronic obstructive pulmonary disease (COPD) ranks third behind ischaemic heart disease and stroke as a major cause of disability and early death in Australia (see the box on this page). Yet, COPD has received much less public and research attention than other respiratory diseases, such as asthma.

COPD is characterised by airflow obstruction due to chronic bronchitis or emphysema; airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.[1] It costs Australia about $800 million a year in direct and indirect costs – hospital admissions, expensive treatments (e.g. mechanical ventilation, long term oxygen therapy), lost years of life, disability, loss of working capacity and reduction in quality of life.[2] Yet, there is no effective pharmacological treatment to attenuate the accelerated decline in lung function seen in patients with COPD. Smoking cessation is the only proven intervention (see the box on this page).

While inhaled corticosteroids are a very effective treatment for asthma, they are also widely used to treat COPD despite limited evidence to support their use. Using inhaled corticosteroids in patients with COPD is costly, local side effects are common, and there is emerging evidence to suggest that they may be associated with systemic side effects. This has led to a reassessment of the use of high doses of inhaled corticosteroids in the management of COPD.

## A difficult diagnosis

It is important to recognise and correctly diagnose COPD early, before disability ensues. While COPD diagnosis is not the main focus of this article, it is important to differentiate COPD from asthma. Community studies have suggested that primary care physicians may have difficulties in distinguishing between these two conditions, and that they often do not base their 'diagnosis' on clinical factors such as bronchodilator reversibility.[3,4] About 33% of respiratory patients living in the community who are currently labelled 'asthmatic' may be more appropriately diagnosed as having COPD.[3,4] The Thoracic Society of Australia and New Zealand is working with other bodies to develop guidelines on COPD diagnosis and management.

Differential diagnosis is complicated by overlapping symptoms and signs relating to the type of airways obstruction, the degree of bronchial hyperreactivity, and other factors. For example, obstruction in many patients with COPD may include a significant reversible component. Conversely, people with asthma may develop irreversible airflow obstruction indistinguishable from COPD.

Many COPD signs and symptoms are nonspecific and can also occur in other conditions, such as congestive heart failure and vocal cord dysfunction. Furthermore, long term smokers may develop late-onset asthma, and may be misdiagnosed as having COPD rather than asthma (reversible airways obstruction), albeit with a significant smoking history.

## Spirometric evaluation

The first step in evaluating overall lung health is spirometry. In patients with COPD, collapsible airways and decreased elastic recoil contribute to the obstructive spirometric picture. The ratio of the $FEV_1$ (forced expiratory volume in one second) to FVC (forced vital capacity) is often used to assess patients for airflow obstruction. It is normally 75 to 85%.

Spirometry in patients with obstructive lung disease shows a reduction in $FEV_1$ to less than 80% of the predicted value, and the $FEV_1$/FVC ratio is less than 70% predicted. Patients with pure COPD do not demonstrate significant bronchodilator reversibility (improvement in $FEV_1$ by at least 12 to 15% and/or greater than 200 mL) and have little variability in serial peak expiratory flow measurements; these are often of little use in

### COPD in brief

- More than half a million Australians suffer from moderate or severe COPD.
- Some 4000 to 5000 of Australians die from the condition each year.
- Smoking is a major risk factor for COPD but only 15 to 20% of smokers develop COPD.
- Although COPD mortality is higher in men, the number of women with COPD is expected to exceed that of men by the year 2005, reflecting the increasing number of women who smoke.
- Smoking cessation is the only effective means of reducing the rate of progression of airways obstruction.

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assessing patients with COPD. However, there is some overlap between COPD and asthma. For example, a minority of patients have radiological evidence of emphysema and permanent lung destruction but also exhibit bronchodilator reversibility.

Testing corticosteroid reversibility (using the same lung function criteria outlined above) is important in patients with moderate to severe disease ($FEV_1$ less than 60% predicted). $FEV_1$ should be measured before and after a trial of oral prednisolone (30 mg daily for two weeks) or inhaled corticosteroid (e.g. beclomethasone 500 µg twice daily or equivalent for six weeks). Corticosteroid reversibility occurs in 10 to 20% of patients with clinically stable COPD.[5] Corticosteroid reversibility must be confirmed by spirometry (preferably formal laboratory testing) including $FEV_1$ and FVC, not simply peak expiratory flow measurements.

## Corticosteroids for COPD

The use of corticosteroids for COPD can be divided into their use for acute exacerbations and for long term maintenance therapy.

### Acute exacerbations

Although corticosteroids are efficacious in patients with exacerbations of asthma, their role in COPD is less clear. Inhaled corticosteroids have not demonstrated the same efficacy as oral/intravenous corticosteroids in acute exacerbations of COPD. The use of oral and intravenous corticosteroids in COPD is supported by data from a double-blind, randomised, controlled study of 271 patients who had an exacerbation of COPD and required hospital admission.[6] Treatment with high dose intravenous corticosteroids (methylprednisolone 125 mg six hourly for 72 hours) followed by oral corticosteroids (60 mg daily for four days, then a reducing course over seven weeks or eight days) resulted in fewer treatment failures, better lung function and shorter hospital stays. Treatment for a total of eight weeks was not superior to treatment for two weeks. These results were supported by Davies and colleagues, who found that 30 mg prednisolone daily for two weeks in patients with exacerbations of COPD requiring hospital admission was associated with better lung function (increased $FEV_1$) and shorter hospital stays.[7]


IMAGE BANK

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However these observations should not be taken as an indication for long term systemic corticosteroid therapy.

### Recommendations

On current evidence, and until definitive guidelines are drawn, low dose oral corticosteroids (prednisolone, 30 mg or 0.6 mg/kg daily for two weeks) is recommended for acute exacerbations of COPD.

### Long term maintenance therapy

A significant $FEV_1$ response to corticosteroid treatment would justify the regular administration of inhaled corticosteroids, according to the British Thoracic Society guidelines for COPD management;[5] however, the Society does not support their use where there is no significant reversibility. The paucity of placebo-controlled trials to assess the efficacy of inhaled corticosteroids in chronic COPD has not supported their use. Several recent controlled trials have examined the effect of inhaled corticosteroids on the rate of $FEV_1$ decline, frequency of exacerbations, health related quality of life and post-bronchodilator $FEV_1$. These studies have attempted to rigorously exclude patients with asthma; however, about 10% of COPD patients will also have some degree of asthma, and it seems likely the responders in these trials will have asthma.

The three largest studies to examine the effect of inhaled corticosteroid therapy in patients with COPD include the EUROSCOP[8] and ISOLDE[9] studies, and a trial that forms part of the Copenhagen City Heart Study. All three studies showed that inhaled corticosteroids had no effect on the long term decline in $FEV_1$ seen in patients with COPD.

The Copenhagen study comprised patients with mild disease, 76% of whom were current smokers, and excluded patients with a steroid response (5% of patients). Inhaled budesonide (800 µg daily) did not improve any outcome measure.

All patients in the EUROSCOP study were current smokers and had a mean $FEV_1$ of 77% predicted. Treatment with the inhaled corticosteroid budesonide 400 µg twice daily via Turbuhaler resulted in an initial improvement in lung function; however, lung function declined at similar rates to those taking placebo.

The ISOLDE study involved patients with more severe COPD

(mean $FEV_1$ of 50% predicted) including current and ex-smokers. Although there was no significant attenuation in the decline of lung function, there was a significant reduction in the number of clinical exacerbations in the corticosteroid treated group (fluticasone 1000 μg daily); clinical exacerbation was defined as a worsening of respiratory symptoms requiring treatment with corticosteroids or antibiotics, as judged by a primary care physician. There was also a significant attenuation in decline of health status as measured by a disease-specific questionnaire. ISOLDE also showed that exacerbations were more likely to occur in patients withdrawn from inhaled corticosteroids than in matched patients who had not been chronically treated with inhaled corticosteroids. These observations are currently unexplained and require further study.

In another study, Paggiaro and colleagues found a significant reduction in moderate to severe exacerbations between patients in the placebo group compared with those treated with fluticasone 500 μg twice daily (86% *v.* 60%, $p<0.001$); lung function also improved after six months.[10] Interestingly, there was a significant reduction in median daily cough and sputum volume with fluticasone, and this may underlie some of the beneficial effects of inhaled corticosteroids for the treatment of COPD.

### Recommendations

In patients with COPD but no asthmatic component, maintenance therapy with inhaled corticosteroids may reduce the frequency of clinical exacerbations and improve the patient's quality of life despite the unrelenting progressive course of the disease. However, these findings need more stringently defined criteria and further attention before specific recommendations can be made.

The patients most likely to benefit are those with moderate to severe disease especially those with $FEV_1$ of 50% or less than predicted (pre-bronchodilator $FEV_1$ less than 1.3 L). The dose of inhaled corticosteroid may be important. The benefits have been seen with the equivalent of fluticasone 1 mg daily. There is no evidence that using lower doses of inhaled corticosteroids are beneficial.[11] There is no attenuation in the long term decline in $FEV_1$ in COPD and there is no evidence of benefit in patients with mild disease ($FEV_1$ greater than 60% predicted or greater than 1.5 L).

Until more definitive evidence of the benefits of inhaled corticosteroid treatment is available and guidelines are drawn, it may be reasonable to use inhaled corticosteroids in patients with severe COPD, particularly those with recurrent exacerbations, and possibly symptomatic patients with disease-related poor social function and quality of life.

## Adverse effects

An increased rate of skin bruising but no decrease in bone density was noted in the EUROSCOP study in patients taking inhaled corticosteroids; there was a small increase in dysphonia, local throat irritation and oral candidiasis. There was also no difference in the number of new diagnoses of hypertension, cataracts, myopathy or diabetes between treatment and placebo groups.[8] The ISOLDE study, which used the highest dose of inhaled corticosteroid, showed a small but significant decrease in mean cortisol concentrations in the treatment group but no more than 5% of patients had values below the normal range; there were apparently no signs or symptoms of hypoadrenalism.[9] The Copenhagen study reported no significant differences in adverse effects between the treatment and placebo groups. The study by Paggiaro and colleagues revealed an overall reduction in mean serum cortisol in the fluticasone group but this was apparently not associated with any clinical effects.[10]

**High dose inhaled corticosteroids should be used cautiously, especially in elderly patients.**

Further assessment of the risks to benefits in the long term is required. This includes assessment of the long-term effects of high doses of inhaled corticosteroids on bone density, although an increase in fracture rate has not been observed in current studies.

Nevertheless, high dose inhaled corticosteroids should be used cautiously, especially in elderly patients, who are at an increased risk of cataracts.[12]

## Conclusions

Doctors should identify COPD early in susceptible individuals and encourage smoking cessation as once established, there are no pharmacological treatments that slow down progression of the disease. Recent studies, however, have shown that inhaled corticosteroids may decrease exacerbations and improve quality of life in some patients with COPD. These benefits must be weighed against potential side effects of long term corticosteroid use; further studies are needed to assess these risks.

An assessment of the patient's ability to use drug delivery devices may be important in the decision to initiate or continue inhaled corticosteroid treatment, as many patients in this age group (especially those aged more than 65 years) may not use their inhalers optimally. If withdrawal of inhaled corticosteroid treatment is indicated, this should be gradual; abrupt cessation may increase the likelihood of short term clinical exacerbations.

Finally, pulmonary rehabilitation (for example, education, exercise training, nutritional support and psychosocial support) should have higher priority in the management of COPD to maintain an individual's maximum level of function and independence. MT

*A list of references is available on request to the editorial office.*

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