Using a combination of fluticasone/salmeterol in the treatment of COPD

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Fluticasone/salmeterol combination therapy should be considered in every patient with moderate or severe COPD who is not adequately controlled on other therapy.

What is fluticasone/salmeterol combination therapy?

Fluticasone/salmeterol (Seretide) is a combination of a long-acting beta$_2$ agonist salmeterol and an inhaled corticosteroid fluticasone. It is available in a dry powder form (Seretide Accuhaler) or in a CFC-free inhaler (Seretide MDI). The indication to prescribe fluticasone/salmeterol has recently been extended from asthma to include chronic obstructive pulmonary disease (COPD).

In whom should it be considered?

The PBS prescription (restricted benefit) guidelines state that 'Seretide is indicated for the symptomatic treatment of COPD where the FEV_1 is less than 50% predicted normal and there is a history of repeated exacerbations with significant symptoms despite regular beta$_2$ agonist bronchodilator therapy.'

What needs to be considered before prescribing it?

Before prescribing fluticasone/salmeterol combination therapy, the diagnosis of COPD needs to be confirmed by a consistent clinical history and spirometry showing a reduced FEV_1 and FEV_1/FVC ratio after bronchodilator therapy.

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A typical history of a patient with COPD will reveal exertional dyspnoea, which is often slowly progressive over time, usually in a current or ex-smoker who has accrued at least a 10-pack year history (one pack year = 20 cigarettes per day for one year). However, it should be noted that COPD can be present in non-smokers exposed to significant atmospheric pollution (including passive tobacco smoking), in nonsmokers or smokers with alpha-1 antitrypsin deficiency or in nonsmokers with a history of recurrent childhood infection. Additional symptoms include intermittent cough, wheeze and sputum production, particularly in association with respiratory tract infections.

Spirometry should be performed before and after bronchodilator therapy. To confirm a diagnosis of COPD, post-bronchodilator therapy spirometry should reveal an FEV_1 of less than 80% of predicted and an FEV_1/FVC ratio of less than 70%. If airways obstruction corrects after bronchodilator therapy to an FEV_1 of greater than 80% predicted and the FEV_1/FVC ratio improves to greater than 70%, asthma is the most likely diagnosis.

Current evidence suggests that fluticasone/salmeterol combination therapy is most beneficial in patients with moderate or severe COPD. In Australia, COPD-X guidelines (described below) classify COPD as moderate if post-bronchodilator FEV_1 is 40 to 59% of predicted and severe if post-bronchodilator therapy FEV_1 is less than 40% of predicted. Australian prescription guidelines reflect the evidence base and appropriately recommend the use of this medication only in patients with moderate or severe COPD.

What are the benefits?

Trials have revealed significant benefits of fluticasone/salmeterol combination therapy compared with its individual components and standard therapy (short-acting bronchodilators) in patients with moderate or severe COPD. Expected benefits of the combination therapy include improvement in symptoms, quality of life (QOL) and lung function, a significant reduction in exacerbations (number needed to treat [NNT] to prevent an exacerbation per year = 4) and hospitalisations (NNT to prevent a hospitalisation per year = 32).[1]

Evidence also suggests a possible survival advantage. The risk of death over three years in the combination group (fluticasone/salmeterol therapy) as compared with placebo (short-acting bronchodilators) was reduced by 17.5% (p=0.052).[1] The risk of death over two years in another study comparing fluticasone/salmeterol and tiotropium was observed to be 50% less (3% *v*. 6%, respectively, p=0.032).[2]

Where does it fit with the overall management of COPD?

The Australian Lung Foundation and Thoracic Society of Australia and New Zealand developed guidelines to improve the diagnosis and management of COPD.[3] The guidelines can be summarised by the acronym COPD-X, as described below.

- **C – confirm diagnosis and assess severity.** Spirometry is essential to confirm the diagnosis of COPD, differentiate it from other conditions such as asthma, and grade the severity of COPD, which subsequently helps determine appropriate therapy.

Table. Medical Research Council dyspnoea scale*

Grade	Degree of dyspnoea
Grade 1	Breathless only with strenuous exercise
Grade 2	Short of breath when hurrying or walking up a slight hill
Grade 3	Walks slower than most people of the same age because of breathlessness or stops for breath when walking at own pace on the level
Grade 4	Stops for breath after walking about 100 metres or a few minutes on the level
Grade 5	Too breathless to leave the house or breathless when dressing

*Adapted from Fletcher CM, Elmes PC, Fairbairn MB, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. BMJ 1959; 2: 257-266.

- **O – optimise function.** All symptomatic patients with COPD (mild, moderate and severe) qualify for therapy with short-acting beta$_2$ agonists. These patients also qualify for tiotropium (Spiriva) with expected benefits to include improvement in dyspnoea, QOL and lung function, and fewer COPD exacerbations.[4,5] Tiotropium is superior to ipratropium and salmeterol.[6] Tiotropium is equivalent to fluticasone/salmeterol with respect to reductions in COPD exacerbations.[2] In patients with moderate or severe COPD, the addition of fluticasone/salmeterol to tiotropium (compared with tiotropium alone) further improves QOL, lung function and hospitalisation rates.[7] Therefore, fluticasone/salmeterol can be taken either:
  - as add-on therapy in patients with suboptimally controlled moderate to severe COPD, who are already taking short-acting beta$_2$ agonists and tiotropium; or
  - with short-acting beta$_2$ agonists if tiotropium is not tolerated or contraindicated.

  To optimise function, pulmonary rehabilitation should also be considered in every patient with moderate or severe COPD. Benefits of pulmonary rehabilitation include reducing dyspnoea, improving emotional function, QOL and exercise capacity, and possibly reducing hospitalisations.[8,9]
- **P – prevent deterioration.** This includes nonpharmacological and pharmacological methods to assist smoking cessation and appropriate use of respiratory infection vaccinations.
- **D – develop a support network and self-management plan.** This includes emergency plans for the appropriate use of antibiotics and brief courses of oral corticosteroids in the event of acute infective exacerbations of COPD.
- **X – manage exacerbations.** This includes the appropriate use of antibiotics and oral corticosteroids for infective exacerbations; identification of possible noninfective comorbidities, which may contribute to exacerbations including cardiac dysfunction and pulmonary thromboemboli; hospitalisation when needed, and use of noninvasive positive pressure ventilation to manage acute hypercapnic respiratory failure.

How to prescribe

A combination of fluticasone/salmeterol (Accuhaler or MDI) can be used in patients with COPD. The dose is one inhalation twice a day of the Seretide Accuhaler 500/50 preparation (fluticasone 500 µg, salmeterol 50 µg) or two inhalations twice a day of the Seretide MDI 250/25 preparation (fluticasone 250 µg, salmeterol 25 µg). Alternatively, if there are concerns about corticosteroid dose, prescription guidelines allow one inhalation twice a day of the Seretide Accuhaler 250/50 preparation (fluticasone 250 µg, salmeterol 50 µg) or two inhalations twice day of Seretide MDI 125/25 preparation (fluticasone 125 µg, salmeterol 25 µg). As the large COPD trials used the larger doses of this medication, there is no evidence to support the lower doses of the Seretide Accuhaler 100/50 or Seretide MDI 50/25 preparations.

How is progress monitored?

Clinical progress of patients taking fluticasone/salmeterol combination therapy can be monitored by assessing:

- changes in dyspnoea
- general wellbeing (as a measure of QOL)
- exacerbation frequency
- lung function tests (however, clinical improvement may occur in the absence of improved lung function).

Changes in dyspnoea may be assessed by using a modified Medical Research Council dyspnoea scale (Table), or by monitoring improvement in a relevant physical activity.

Failure to improve should prompt inquiry about compliance with treatment, correct use of the Accuhaler or MDI and a search for unrecognised or inadequate treatment comorbidities (which may include hypoxia requiring domiciliary oxygen, cor pulmonale with right heart failure, bronchiectasis, ischaemic heart disease, left ventricular dysfunction or obstructive sleep apnoea). In these situations, specialist referral of the patient may be needed.

Side effects

Oral candidiasis and dysphonia are potential side effects of any inhaled preparation containing an inhaled corticosteroid. The frequency of these side effects can be lessened by instructing patients to rinse,

gargle and spit after using their inhaler, and by using a spacer with MDI preparations.

In the largest COPD study conducted over three years, patients in the treatment arm receiving fluticasone/salmeterol did not develop new cataracts or new non-traumatic fractures significantly more frequently than the placebo group (fluticasone/salmeterol *v.* placebo: nontraumatic fractures 1.7% *v.* 1.8%; cataracts 27% *v.* 21%, respectively).[1] However, the risk of developing fractures in this population group remains significant, and at baseline (enrolment before study) 44% of patients had cataracts, underlying the need for practitioners to appropriately consider osteoporosis/fracture risk and eye disorders in any patient with moderate or severe COPD.

Two large studies have shown that, despite overall benefits including a reduction in exacerbations, there is an increased risk of developing pneumonia in patients with moderate or severe COPD who are receiving therapies including inhaled corticosteriods.[1,2] The message here is not to discontinue fluticasone/salmeterol, but rather to search for underlying factors that may lead to lower respiratory tract infections. Considerations should include unusual or resistant organisms colonising the airways, mucus impaction, bronchiectasis or possibly underlying malignancy contributing to slow-to-resolve or recurrent respiratory tract infection. Sputum cultures, CT thorax or specialist referral should be considered in patients with slow-to-resolve or recurrent respiratory tract infection.

Important precautions and interactions

The fluticasone/salmeterol combination is not an acute reliever medication. Short-acting beta$_2$ agonists remain the choice of treatment to relieve acute symptoms. Fluticasone/salmeterol is superior to its individual component elements in the treatment of COPD, so there is little role for the prescription of salmeterol or fluticasone alone in the treatment of moderate or severe COPD.

Fluticasone/salmeterol may be prescribed in addition to tiotropium in the treatment of moderate or severe COPD. If tiotropium is co-prescribed, other anticholinergics such as ipratropium should be discontinued. Tiotropium, an anticholinergic agent, should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy and bladder neck obstruction. Cessation of inhaled-containing preparations in patients with moderate or severe COPD may lead to clinical deterioration and recurrent exacerbations.[10,11] Therefore, close clinical monitoring is recommended if fluticasone/salmeterol is withdrawn for any reason.

Conclusion

Fluticasone/salmeterol combination therapy is now indicated for the treatment of COPD. It should be considered in every patient with moderate or severe COPD who is not adequately controlled on other therapy. However, fluticasone/salmeterol is only one component of the management of COPD. All elements of the COPD-X guidelines should be considered at the same time as initiating this medication. All practitioners managing patients with COPD should have access to a spirometer (either in their rooms or by referral) and be familiar with the COPD-X guidelines (for more information on these guidelines visit: www.copdx.org.au). MT

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COMPETING INTERESTS: Dr Rice-McDonald sits on Medical Advisory Boards for GlaxoSmithKline, AstraZeneca and Boehringer Ingelheim.