Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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COPD: risk of pneumonia with 2 different inhaled corticosteroid/LABA combinations

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A large observational study has found that use of fluticasone dipropionate/salmeterol in people with chronic obstructive pulmonary disease (COPD) was associated with a greater risk of pneumonia, and of death associated with pneumonia, than budesonide/formoterol. The study reinforces MHRA advice to be vigilant for the development of pneumonia and other infections of the lower respiratory tract when using inhaled corticosteroids to treat people with COPD, and to follow NICE guidance for the care of people with COPD.

Overview and current advice

NICE guidance on the management of COPD recommends inhaled corticosteroids (ICS) in combination with other inhaled therapies for selected patients, as part of the range of treatment options. The guidance advises practitioners to be aware of the potential risk of side effects (including non-fatal pneumonia) in people with COPD treated with ICS, and to be prepared to discuss this risk with patients.

The MHRA has advised that treatment with an ICS in COPD – either alone or in combination with a long-acting beta-agonist (LABA) – significantly increases the risk of pneumonia (although in clinical trials there was no associated increase in the rate of mortality due to pneumonia). In the TORCH study the probability of pneumonia was 19.6% in the salmeterol/fluticasone dipropionate group and 18.3% with fluticasone alone compared with 12.3% in the placebo group. The MHRA recommends that ICS should not be used alone in COPD. Although in all trials combination therapy was more effective than monotherapy, the benefit is variable and not always clinically relevant and the MHRA advises that ICS should be introduced only when COPD progresses to severe disease, in line with NICE guidance.

Only ICS in combination inhalers are licensed for treating COPD. Two products are currently licensed for this indication: Seretide Accuhaler (fluticasone dipropionate with salmeterol) and Symbicort (budesonide with formoterol).
See the NICE Evidence topic page on COPD and the Clinical Knowledge Summary for a general overview of the condition. The NICE Pathway: COPD brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A retrospective cohort study has compared the rates of pneumonia associated with fluticasone dipropionate/salmeterol and budesonide/formoterol using data from the Swedish national registries of people with COPD. Patients eligible for inclusion were those of any age with a diagnosis of COPD who received these treatments between January 1999 and December 2009. Propensity scoring was used to derive 2 matched cohorts of 2734 people each, taking into account a large number of variables including age, sex, available lung function measurements, drug therapy (including antibiotics and oral corticosteroids), certain comorbid conditions, and number of previous admission to hospital.

The rate of diagnosis of pneumonia per 100 patient years was 11.0 in the fluticasone dipropionate/salmeterol cohort and 6.4 in the budesonide/formoterol cohort (rate ratio 1.73, 95% confidence interval [CI] 1.57 to 1.90, \( p < 0.001 \)). The corresponding number needed to treat (NNT) to avoid 1 pneumonia event per year was 23 (95% CI 18 to 37).

The rate of admission to hospital due to pneumonia per 100 patient years was statistically significantly higher in the fluticasone dipropionate/salmeterol cohort (7.4 compared with 4.3, rate ratio 1.74, 95% CI 1.56 to 1.94, \( p < 0.001 \)), as was the number of days in hospital because of pneumonia (52.8 days compared with 29.0 days per 100 patient years, rate ratio 1.82, 95% CI 1.62 to 2.05, \( p < 0.001 \)). Patients who received fluticasone dipropionate/salmeterol were statistically significantly more likely to die from causes related to pneumonia than those who received budesonide/formoterol (hazard ratio [HR] 1.76, 95% CI 1.22 to 2.53, \( p = 0.003 \)). However, there was no statistically significantly difference in the overall risk of death between the 2 cohorts (HR 1.08, 95% CI 0.93 to 1.14, \( p = 0.59 \)).

When analysed by burden of disease, the risk of pneumonia was greater in the fluticasone dipropionate/salmeterol cohort than in the budesonide/formoterol cohort in all quartiles (based on baseline propensity score). Moreover, the between-treatment difference in risk was observed to be greater in people with a greater burden of disease: for example, the relative risk of pneumonia (fluticasone dipropionate/salmeterol compared with budesonide/formoterol) was 1.13 (\( p < 0.08 \), NNT 155 per year) in the quartile with the lowest burden of disease, and 2.09 (\( p < 0.001 \), NNT 23 per year) in the quartile with the highest burden. However, the statistical significance of these between-quartile differences in relative risk was not reported. The higher risk of pneumonia with fluticasone dipropionate/salmeterol than with budesonide/formoterol was independent of whether or not patients had had a diagnosis of pneumonia during the 2 years before the first prescription for the ICS/LABA.

Commentary provided by the NICE Medicines and Prescribing Centre

This study’s strengths include its size (19,170 patient years of follow up) and the duration of patient exposure to the study drugs (more than 3 years on average). In addition, it was based on usual practice in primary care and so is more naturalistic than a randomised controlled trial (RCT). However, unlike in the setting of an RCT, in ‘real life’ treatment plans are chosen,
changed, or actively not chosen in the light of individual patients’ risk factors, preferences and tolerability of or response to other drugs. Thus observed differences in outcomes may be due to differences among the patients, not only the different treatments. In this study the authors adjusted for a large number of such possible confounding factors but it is possible that unknown but relevant factors were not taken into account. These inevitable limitations mean that a single observational study, such as this one, can suggest an association but not prove causation. Moreover, the accuracy of the diagnoses of COPD was not fully verified by spirometry in all cases. There was no standard definition of pneumonia, and radiography and laboratory data were not available for all patients.

Prolonged use of high doses of ICS carries a risk of systemic side effects, including adrenal suppression, decrease in bone mineral density, cataract and glaucoma. ICS have also been associated with a dose-related increased risk of diabetes onset and diabetes progression, and with an increased risk of fracture. The MHRA has reminded health professionals to remain vigilant for the development of pneumonia and other infections of the lower respiratory tract when using ICS to treat people with COPD, because the clinical features of such infections and exacerbations frequently overlap.

This study reinforces the need for healthcare professionals to follow NICE guidance and be aware of the potential risk of side effects in people with COPD treated with ICS and be prepared to discuss these with patients. Because of the risk of systemic side effects, patients who require prolonged high-dose ICS should be issued with a steroid treatment card. Practitioners may wish to bear in mind the results of this study when discussing treatment options with patients.

**Study sponsorship**

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**References**


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