COPD: further evidence on the risk of pneumonia with inhaled fluticasone or budesonide

A large Cochrane systematic review of 43 randomised controlled trials provides further evidence that taking fluticasone or budesonide alone or in combination with a long-acting beta-agonist (LABA) increases the risk of non-fatal serious pneumonia events (requiring hospital admission) in people with chronic obstructive pulmonary disease (COPD). No increase in total mortality was found.

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 (ICS) to treat people with COPD, and supports the approach set out in NICE guidance for the care of people with COPD.

Overview and current advice

NICE guidance on the management of COPD recommends 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 LABA – significantly increases the risk of pneumonia. In the TORCH randomised controlled trial (RCT) the probability of pneumonia was 19.6% in the fluticasone propionate/salmeterol group and 18.3% with fluticasone propionate alone compared with 12.3% in the placebo group. The MHRA recommends that ICS should not be used alone in COPD and that ICS should be introduced only when COPD progresses to severe disease, in line with NICE guidance.

Only ICS in combination inhalers with a LABA are licensed for treating COPD. Three products are currently licensed for this indication: Seretide Accuhaler (fluticasone propionate with salmeterol), Symbicort (budesonide with formoterol) and Relvar Ellipta (fluticasone furoate with vilanterol), the latter being the subject of a NICE Evidence Summary New Medicine.

It is unclear whether the risk of pneumonia varies between different ICS. A meta-analysis of RCTs found more reports of pneumonia with fluticasone than with budesonide in people with COPD. However, firm conclusions are limited by the smaller numbers and shorter durations of budesonide RCTs published in this area and other differences between studies. A large observational study (PATHOS) found that use of fluticasone/salmeterol in people with COPD was associated with a greater risk of pneumonia, and of death associated with pneumonia, than budesonide/formoterol. (See previous Medicines Evidence Commentary for a discussion of this study and its limitations). A recent large Canadian observational study provided additional evidence that taking ICS increases the risk of serious pneumonia in people with COPD. Fluticasone was associated with a greater risk of...
serious pneumonia than budesonide, but this might have been due to differences between the people who were assigned to each drug (see previous Medicines Evidence Commentary).^4^ 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

This Cochrane systematic review (Kew KM, Seniukovich A, 2014)^5^ of 43 double-blind RCTs assessed the risk of pneumonia associated with the use of inhaled fluticasone and budesonide for COPD. It included 17 RCTs (n=10,150) of budesonide and 26 RCTs (n=21,247) of fluticasone (propionate or furoate) used either alone or in combination with a LABA in people with COPD. (The LABAs used were formoterol with budesonide, and salmeterol or vilanterol with fluticasone). Studies ranged from 3 to 36 months. Evidence from the budesonide studies was more imprecise and inconsistent and the studies were shorter than the fluticasone studies. Most participants (around three-quarters) were men, mean age was 63 years, the mean predicted FEV$_1$ was just under 50% and smoking ranged from 27 to 63 pack-years (number of pack-years = [number of cigarettes smoked per day × number of years smoked]/20). The primary outcome, non-fatal serious pneumonia events (requiring hospital admission) was statistically significantly increased with fluticasone (odds ratio [OR] 1.78, 95% confidence interval [CI] 1.50 to 2.12; 17 RCTs, n=19,504); budesonide also increased the risk of pneumonia (OR 1.62, 95% CI 1.00 to 2.62; 7 RCTs, n=6,472) compared with control but the effect was less precise and based on shorter trials. Fluticasone was associated with 18 more episodes of non-fatal serious pneumonia per 1000 patients treated over 18 months and budesonide was associated with 6 more episodes per 1000 patients treated over 9 months. The analysis was based on studies of ICS used alone or in combination with a LABA compared with placebo or a LABA.

The outcome for fluticasone was rated by the authors as high quality and it was not statistically significantly different when considering its use as monotherapy (against placebo) compared with its use in combination with a LABA (against LABA alone) or when considering different dose, trial duration or baseline severity. The budesonide outcome was rated as moderate quality. The authors suggested that some of the inconsistencies in the budesonide data might be explained by the fact that a statistically significant increase in non-fatal serious pneumonia was seen with the 640 micrograms per day dose (OR 2.02, 95% CI 1.15 to 3.57) but not with 320 micrograms per day (OR 0.68, 95% CI 0.27 to 1.71).

Neither budesonide nor fluticasone were associated with a statistically significant increase in the secondary outcomes of all-cause mortality or all non-fatal serious adverse events compared with control. Pneumonia-related deaths were too rare for conclusions to be drawn. However, all pneumonia events were statistically significantly increased with fluticasone (OR 1.68, 95% CI 1.49 to 1.90) but not with budesonide (OR 1.12, 95% CI 0.83 to 1.51).

Indirect comparisons of ICS monotherapy found no statistically significant differences between fluticasone and budesonide in non-fatal serious pneumonia (low-quality evidence), all-cause mortality (low-quality evidence) or all non-fatal serious adverse events (moderate-quality evidence). The only statistically significant difference between ICS was in all pneumonia events. This was more common with fluticasone than budesonide (OR 1.86, 95% CI 1.04 to 3.34), but had wide confidence intervals. The authors suggested that this finding should be interpreted with caution because of possible differences in assignment of a diagnosis of pneumonia, and because no trials directly compared the 2 drugs. Furthermore, there was no longer a statistically significant difference after sensitivity analysis removed the TORCH RCT^1^, which dominated the pneumonia events with fluticasone.
**Commentary**

This systematic review supports earlier RCTs, meta-analyses and observational studies in showing an increase in the risk of pneumonia with budesonide and fluticasone in COPD. This study’s strengths include that it is a good quality systematic review of RCTs involving large numbers of patients with COPD (over 25,000 for the primary outcome). While most of the budesonide and fluticasone studies were funded by 2 different pharmaceutical companies, the authors did not identify any differences in study conduct between them. An important limitation is that evidence from the budesonide studies was more imprecise and inconsistent and the studies were shorter than the fluticasone studies. In addition, none of the included trials were designed to measure the incidence of pneumonia and so its definition and method of diagnosis were usually missing. The authors note that it is not known how much misclassification there might have been between pneumonia events and acute exacerbations of COPD. Allocation concealment was not well reported in the studies. A further limitation is that, for the indirect comparison, all doses of budesonide and fluticasone were pooled and the study was unable to account for the dose-related effects that were seen with budesonide, or for any differences in dose equivalence between the 2 ICS.

Previous published studies have often reported a higher risk of serious pneumonia with fluticasone than with budesonide, but there have been limitations to the data. This systematic review did not find a statistically significant difference between fluticasone and budesonide in the risk non-fatality of serious pneumonia. However, the authors were only able to compare budesonide and fluticasone as monotherapy. This may not reflect current UK practice, where only certain combination products of ICS with a LABA are licensed for COPD (see Overview and current advice). Furthermore, there were no head-to-head RCTs identified and the quality of this particular finding is limited by the nature of indirect comparisons.

Prolonged use of high doses of ICS carries a risk of systemic side effects, including adrenal suppression, decrease in bone mineral density, cataracts 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.

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**References**

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