Cochrane review: Inhaled corticosteroids and risk of pneumonia in chronic obstructive pulmonary disease (COPD)

Kayleigh Kew, Chris Cates

Cochrane Airways Group, Population Health Research Institute

The Cochrane Collaboration
Trusted evidence. Informed decisions. Better health.

Background

Inhaled corticosteroids (ICS) are anti-inflammatory drugs that can reduce the occurrence of COPD flare-ups and improve quality of life. In COPD, ICS are commonly used alongside long-acting beta$_2$-agonists (LABA).

Many studies have shown benefits of ICS, but they can also increase the risk of pneumonia which can be difficult to diagnose, and is often poorly reported in trials.

Objective

To assess the risk of pneumonia associated with the use of fluticasone and budesonide for COPD.

Methods

We searched electronic databases, trial registration sites, reference lists, previous reviews and drug company registries, and contacted trial authors for unpublished data. The last search was done in September 2013.

We included studies comparing budesonide or fluticasone (furoate or propionate) to placebo, and all studies comparing their use in combination with a LABA to LABA alone. This allowed us to assess the risk of ICS used alone or as combination therapy.

We also conducted an indirect comparison of budesonide and fluticasone using their relative effects against placebo, to explore whether one drug was safer than the other.

Results

We found 43 studies including more than 30,000 people with COPD. More studies used fluticasone (26 studies; 21,247 people) than budesonide (17 studies; 10,150 people), and more fluticasone studies tested the propionate formulation than furoate. More people in the studies were male (around 70%), and their COPD was mostly severe. Differences between ICS used alone or in combination with a LABA were not significant so pooled results are presented.

Fluticasone increased 'serious' pneumonias (those requiring hospital admission; **Fig. 1**, 4.1.1). Over 18 months, 18 more people of every 1000 treated with fluticasone were admitted to hospital for pneumonia (**Table 1**).

Budesonide also increased pneumonias that were classed as 'serious' (**Fig. 1**, 4.1.1). Over nine months, six more hospital admissions were reported for every 1000 individuals treated with budesonide (**Table 1**).

No more deaths overall were reported in the ICS groups compared with controls (**Fig. 1**, 4.1.2), and deaths related to pneumonia were too rare to tell (**Fig. 1**, 4.1.3).

Comparing fluticasone and budesonide (**Fig. 2**), the difference was not clear enough to tell whether one was safer for most outcomes (serious cases of pneumonia, adverse events, and mortality). The risk of having any pneumonia event (i.e. less serious cases treated out of hospital) was higher with fluticasone than with budesonide (**Fig 2**, 1.1.4).

Evidence was rated high or moderate quality for most outcomes. Budesonide results were generally less clear as they were based on fewer people and shorter studies.

Table1. Summary of findings table for each ICS versus controls (mono- and combination therapy trials combined) – pneumonia requiring hospital admission

Outcomes Follow-ups presented as weighted means	Illustrative comparative risks* (95% CI) Assumed risk Control	 Corresponding risk Fluticasone	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
Fluticasone					
Non-fatal, serious adverse pneumonia events (requiring hospital admission) Follow-up: 18 months	**25 per 1000**	**43 per 1000** (37 to 51)	**OR 1.78** (1.50 to 2.12)	19,504 (17 studies)	⊖⊖⊖⊖ **high**
Budesonide					
Non-fatal, serious adverse pneumonia events (requiring hospital admission) Follow-up: 9 months	**9 per 1000**	**15 per 1000** (9 to 24)	**OR 1.62** (1.00 to 2.62)	6472 (7 studies)	⊖⊖⊖⊖ **moderate**[1,2]

[1]Confidence intervals are quite wide but are not considered serious enough to downgrade.
[2]More than half the studies did not report the outcome (-1 for publication bias).

Figure 1. Summary plot showing each ICS versus controls for all outcomes (mono- and combination therapy trials combined). Non-fatal serious adverse pneumonia events were those requiring hospital admission.

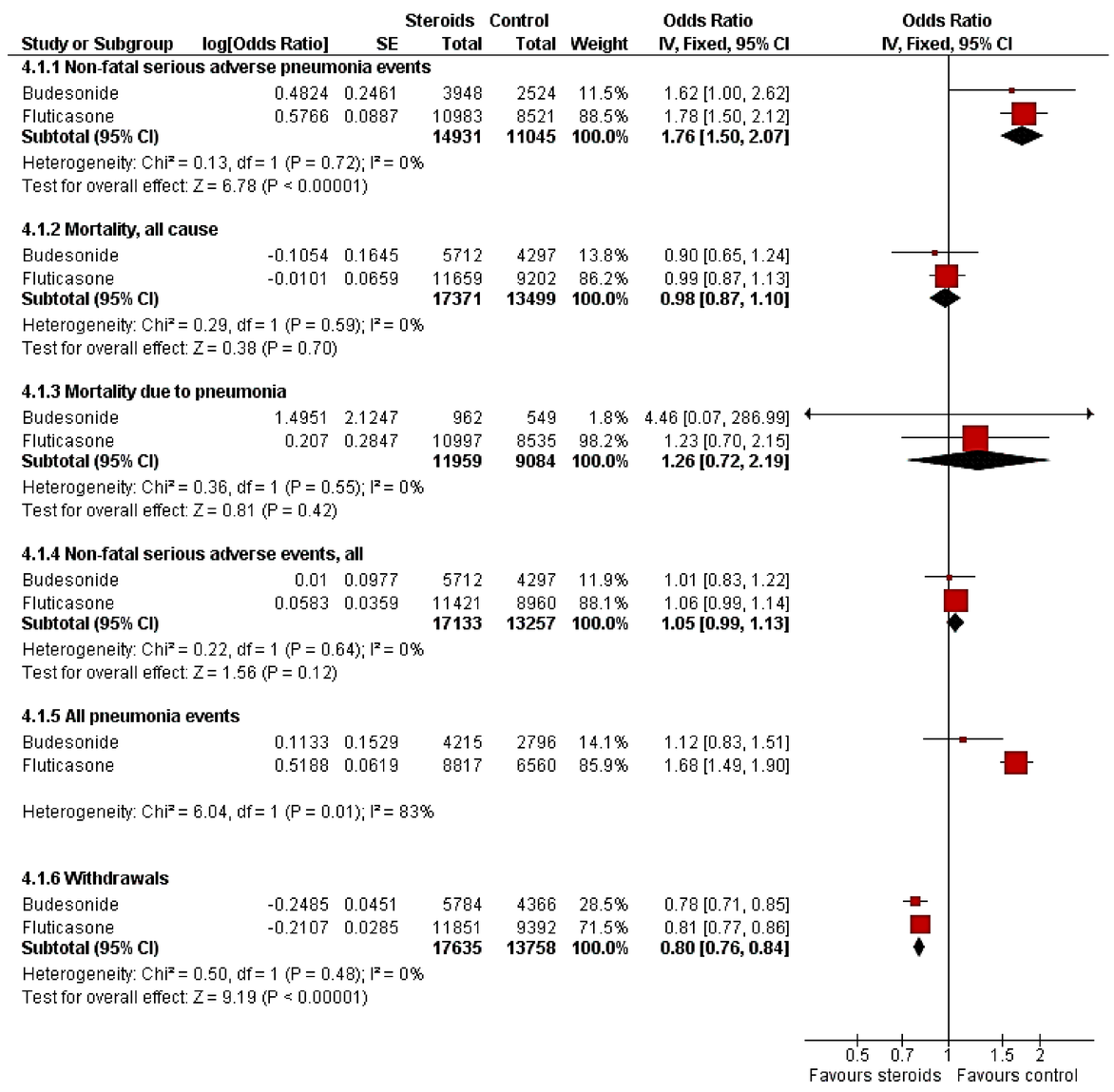
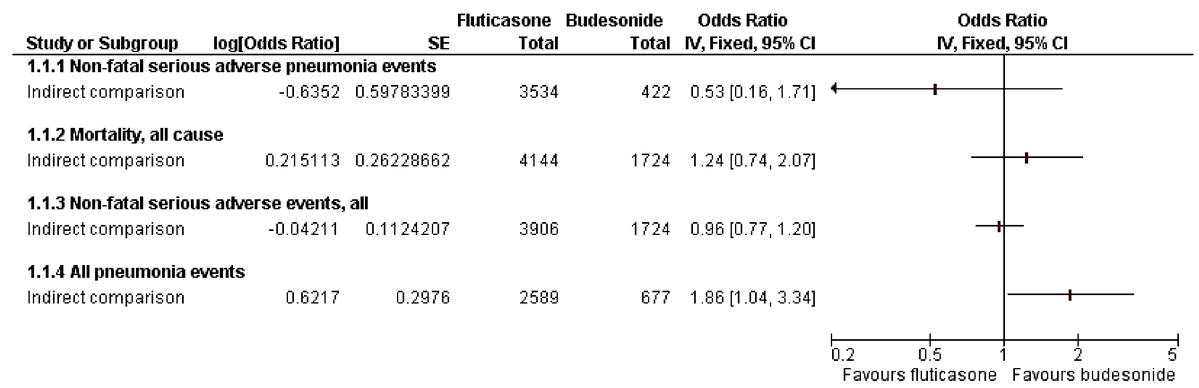


Figure 2. Indirect comparisons of fluticasone and budesonide using relative effects against placebo. Non-fatal serious adverse pneumonia events were defined as those requiring hospital admission.



Conclusion

Budesonide and fluticasone, delivered alone or in combination with a LABA, can increase serious cases of pneumonia that result in hospital admission. Neither has been shown to affect the chance of dying compared with not taking ICS.

Comparison of the two drugs revealed no difference in serious cases of pneumonia or risk of death. Fluticasone was associated with a higher risk of any pneumonia (i.e. cases that could be treated in the community) than budesonide, but potential differences in the definition used by the respective drug manufacturers reduced our confidence in this finding. These concerns need to be balanced with the known benefits of ICS (e.g. fewer exacerbations, improved lung function and quality of life).

Researchers should remain aware of the risks associated with ICS and should make sure that pneumonia is properly diagnosed in studies.

CRG Funding Acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Airways Group.