Budesonide/formoterol vs salmeterol/fluticasone in COPD: a systematic review and adjusted indirect comparison of pneumonia in randomised controlled trials

Halpin DM, Gray J, Edwards SJ, Morais J, Singh D

CRD summary
The review of indirect comparisons concluded that budesonide/formoterol was associated with fewer pneumonia events than salmeterol/fluticasone in patients with chronic obstructive pulmonary disease. The authors’ conclusions seem reasonable but reporting limitations mean that cautious interpretation is warranted.

Authors’ objectives
To compare the efficacy of budesonide/formoterol with salmeterol/fluticasone on the incidence of pneumonia adverse events, pneumonia serious adverse events and pneumonia-related mortality in patients treated for chronic obstructive pulmonary disease.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and MEDLINE were searched up to August 2009 for publications in English; search terms were reported. ClinicalTrials.gov and industry trial databases (AstraZeneca and GlaxoSmithKline) were also searched. Relevant systematic reviews identified as part of the literature search were also checked for additional trials.

Study selection
Eligible randomised controlled trials (RCTs) compared budesonide/formoterol or salmeterol/fluticasone with placebo in patients being treated for chronic obstructive pulmonary disease. Patients had to report at least one outcome of interest such as: incidence of pneumonia adverse events, pneumonia serious adverse events or pneumonia-related mortality. The original search was for head-to-head comparisons of budesonide/formoterol with salmeterol/fluticasone but as none were available, a search for trials allowing indirect comparisons was made in accordance to the research protocol.

All trials of budesonide/formoterol used the same medication dose of 320/9 ug bid (320/9 micrograms twice a day) and most trials involving salmeterol/fluticasone used a dose of 50/500 ug bid (one trial used a dose of 50/250 ug bid). The administration of concurrent medication varied across studies. The mean age across groups ranged from 63 years to 66 years, 22% to 61% of participants were current smokers at enrolment and mean baseline forced expiratory volume ranged from 36% to 58% in the active intervention groups and 36% to 59% in the placebo groups, where reported. Study duration ranged from eight to 156 weeks.

The authors did not state how many reviewers were involved in the study selection.

Assessment of study quality
Two reviewers independently assessed trials based on the rigorousness of techniques to minimise the risk of bias with regard to pneumonia outcomes (no further details reported) and results used to decide on trial inclusion.

Data extraction
Data on the incidence of primary outcomes were extracted and used to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Only adverse events, serious adverse events and pneumonia-related mortality with onset during treatment that were reported separately from all events were counted. Where there were two active comparator arms of interest with different dosages, the arm with the greatest homogeneity to other trials and the most clinically relevant comparison was chosen. Where possible, intention-to-treat data were extracted or data were recalculated in an intention-to-treat format. Participants were reinstated into the analysis based on a worst-case scenario if they had received at least one dose of study medication. Where data was not reported in the published study trial, reports on internal or external study databases were used.

One reviewer extracted data which was checked by a second reviewer.
Methods of synthesis
Summary odds ratios and 95% confidence intervals were calculated from the unadjusted odds ratios with associated variances (calculated using the Mantel-Haenzel random-effects method) using the Bucher et al. adjusted indirect comparison method of budesonide/formoterol and salmeterol/fluticasone, with placebo as the common comparator. I², in accordance with Higgins et al., and funnel plots were used to assess heterogeneity and small-study effects. There were no pre-specified subgroup analyses. Sensitivity analysis was reserved for testing the robustness of the conclusions drawn to any assumptions introduced in handling the data.

Results of the review
Twelve RCTs were included in the review (7,680 patients); eight compared salmeterol/fluticasone with placebo (5,205 patients) and four compared budesonide/formoterol with placebo (2,475 patients). No trials were excluded from the analyses on the assessment of risk of bias. All trials were double-blinded. Discontinuation rates ranged from 5% to 34% in the active intervention groups and 5% to 44% in the placebo groups.

The results of the adjusted indirect comparison found that a significantly lower proportion of patients experienced a pneumonia adverse event (OR 0.47, 95% CI 0.28 to 0.80) or a pneumonia serious adverse event (OR 0.41, 95% CI 0.19 to 0.86) with budesonide/formoterol compared with salmeterol/fluticasone. No significant difference between the treatment comparators was found for pneumonia-related mortality. No significant heterogeneity was found in the pairwise meta-analyses.

A sensitivity analysis, excluding one trial in which the salmeterol/fluticasone dose (50/250ug bid) differed from the other trials, was performed; the results did not substantially alter the findings of the primary analyses. Testing for small study effects was not possible.

Authors' conclusions
Results of the indirect comparisons suggested that budesonide/formoterol was associated with fewer pneumonia events than salmeterol/fluticasone in patients with chronic obstructive pulmonary disease.

CRD commentary
The review question was supported by clearly defined inclusion criteria and several relevant databases were searched. The search was restricted to English language publications and so language bias was possible. Appropriate steps were taken to minimise the likelihood of error or bias in the validity assessment and extraction of data but it was not clear if similar steps were taken for study selection. The authors stated that the included trials were assessed for risk of bias but did not provide details so it was unclear what criteria were used.

The synthesis of trials appeared appropriate using standard methods. However, as highlighted by the authors, the results from a single trial had a large influence on the overall findings, there was some clinical heterogeneity in terms of dosing and length of trial, and in terms of pneumonia related mortality the small number of included trials and too few events make firm conclusions difficult. Overall, the authors' conclusions appeared reasonable but reporting limitations meant that cautious interpretation was warranted.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors indicated that the identification of risk factors for the development of pneumonia, as well as more attention to subgroups that were at greater risk of developing pneumonia would be useful. The authors stated that there was a lack of predefined diagnostic standards for pneumonia in the trials identified.

Funding
AstraZeneca UK Ltd.

Bibliographic details
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.