Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review

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CRD summary
This review concluded that compared with long-acting beta-agonist (LABA) monotherapy, the magnitude of benefits of combined LABA/inhaled corticosteroid therapy did not achieve predefined clinically important effects and there were serious side effects. The absence of full quality details (and indications that many trials failed the only reported criterion) made the reliability of the conclusion unclear.

Authors' objectives
To evaluate the safety and efficacy of combined long-acting beta-agonists (LABAs) and inhaled corticosteroids compared with LABA monotherapy in adult patients with chronic pulmonary obstructive disorder (COPD).

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1980 to 2009. Search terms were reported. Drug manufacturers were consulted for further details. Abstracts were excluded. There were no language restrictions.

Study selection
Randomised controlled trials (RCTS) of adult patients over the age of 40 years with stable COPD and who received inhaled LABAs plus inhaled corticosteroids compared with LABA monotherapy were eligible for inclusion. Study duration had to be greater than one month. Patients with COPD had to satisfy diagnostic criteria of American Thoracic Society/European Respiratory Society or the Global Initiative for Chronic Obstructive Lung Disease. The combined intervention had to be delivered by metered dose or dry powder inhaler.

Primary outcomes of interest were: severe COPD exacerbation (required hospitalisation or withdrawals); moderate COPD exacerbations (required systemic corticosteroids or antibiotic use); all-cause mortality; respiratory deaths; and cardiovascular mortality during the period of treatment. Secondary outcomes of interest were mean change in pulmonary function (FEV₁ pre and post bronchodilator therapy); mean change in St George respiratory questionnaire (SGRQ) total score; end-of-treatment dyspnea score; withdrawals; and adverse events.

Included trials evaluated combinations of formoterol/budesonide and salmeterol/fluticasone in doses that ranged from 250μg to 500μg, twice daily. More than half of the included trials were long-term duration (≥52 weeks). Most patients were classified as having moderate to very severe COPD exacerbations. Mean age was 64 years. Most were male (72%). Where reported, a mean of 31% of patients (range 0% to 55%) had received inhaled corticosteroids before.

Three reviewers independently selected trials for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
A quality assessment was reported to be carried out, but only allocation concealment was presented as a criterion.

Three reviewers independently performed quality assessment. Disagreements were resolved by consensus.

Data extraction
Data were extracted to enable calculation of relative risks (RR) and standardised mean differences (SMD), and 95% confidence intervals (CI). The number needed to treat for benefit (NNTB) or number needed to treat for harm (NNTH) were calculated.

Three reviewers independently extracted data. Disagreements were resolved by consensus.
Methods of synthesis
Relative risks and weighted mean differences (WMD) and 95% CIs were pooled in fixed-effect or random-effects meta-analysis (depending on the level of heterogeneity). Statistical heterogeneity was assessed using the $I^2$ statistic.
Publication bias was assessed in funnel plots. Sensitivity analysis was conducted on the primary outcome (severe COPD exacerbations) in terms of: allocation concealment; trial duration; reversibility to short-acting beta-agonists; use of salmeterol or formoterol; and use of inhaled corticosteroids prior to study enrolment.

Results of the review
Eighteen RCTs were included in the review (n=12,446). Allocation concealment was considered to be adequate in five trials. The risk of bias was unclear in 13 trials.

Combination therapy was associated with a significantly decreased risk of moderate COPD exacerbations (RR 0.84, 95% CI 0.74 to 0.96, NNTB 31, 95% CI 20 to 93; 13 trials) and a reduced SGRQ score (WMD -1.88, 95% CI -2.44 to -1.33; eight trials). There was significant heterogeneity (range $I^2=29\%$ to $50\%$) in these analyses.

$\text{FEV}_1$ was significantly increased at pre-bronchodilator therapy (WMD 0.06, 95% CI 0.04 to 0.07; 12 trials) and post-bronchodilator therapy (WMD 0.04, 95% CI 0.02 to 0.05; eight trials). There was significant heterogeneity (pre-bronchodilator therapy $I^2=82\%$ and post-bronchodilator therapy $I^2=64\%$). This outcome was associated with an increased risk of pneumonia (RR 1.63, 95% CI 1.35 to 1.98, NNTH 40, 95% CI 26 to 72; 12 trials; $I^2=20\%$).

Statistically significant lower scores were found for dyspnea and overall withdrawals and statistically higher rates were found for viral respiratory infections and oropharyngeal candidiasis in patients who received combination therapy. Combination therapy did not significantly decrease risk of severe COPD exacerbations, all-cause mortality, respiratory and cardiovascular mortality.

Sensitivity analysis did not materially alter the main findings. The authors stated that publication bias could be ruled out for all-cause, respiratory and cardiovascular mortality, but not for severe COPD exacerbations.

Authors' conclusions
Compared with LABA monotherapy, the magnitude of benefits of LABA/inhaled corticosteroid therapy did not reach that of the criteria for predefined clinically important effects and were associated with serious side effects.

CRD commentary
The review question was clear and supported by inclusion criteria that appeared to be reproducible. The search strategy included some relevant sources. Retrieval of unpublished material and use of articles in any language minimised potential for publication and language biases. The review process was carried out with sufficient attempts to minimise error and bias. The authors stated that a quality assessment was carried out, but this appeared to be limited to one criterion. Study details were provided adequately, heterogeneity was assessed and the chosen methods of synthesis appeared to be appropriate. A number limitations were acknowledged by the authors, including differences in reported outcome definitions. Author connections with various drug manufacturers were declared.

The authors' conclusion reflected the evidence presented, but the absence of full quality details (and indications that many included trials failed the only criterion that was reported) made the reliability of the conclusion unclear.

Implications of the review for practice and research
Practice: The authors stated that most patients with moderate-to-very severe COPD should probably be treated only with LABA monotherapy.

Research: The authors stated that future large prospective studies should evaluate the increased risk of adverse effects following combination LABA/inhaled corticosteroid therapy and use objective definitions of pneumonia.

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