Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD
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CRD summary
This review evaluated the safety and efficacy of anticholinergics and β₂-agonists in chronic obstructive pulmonary disease. The authors concluded that inhaled anticholinergics can significantly reduce the risk of severe exacerbations and respiratory deaths, and that β₂-agonists are associated with increased respiratory deaths. This was a largely well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To evaluate the safety and efficacy of anticholinergics and β₂-agonists in chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched for studies published between 1966 and December 2005; the search terms were reported. Reference lists of relevant reviews and files from the U.S. Food and Drug Administration website were screened for additional studies. There were no language restrictions.

Study selection
Randomised controlled trials of at least 3 months’ duration comparing anticholinergics or β₂-agonists with each other, or with placebo, in patients with COPD were eligible for inclusion. Trials were required to report at least one COPD exacerbation leading to withdrawal from the study or hospitalisation, or any respiratory death. Deaths due to a cardiorespiratory event were included if they were related to COPD. The included β₂-agonists were albuterol, metaproterenol, formoterol and salmeterol. The included anticholinergics were ipratropium and tiotropium. The mean duration of the trials was 20 months, and the mean ages of the patients were 59.9, 63.5 and 59.6 years, respectively, in the anticholinergic, β₂-agonist and placebo groups. Over half of the patients using β₂-agonists were receiving concomitant corticosteroids.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Trial quality was assessed according to randomisation procedure and allocation concealment, blinding, drop-outs and withdrawals, and whether intention-to-treat analysis had been used. Each quality criterion was scored on a 3-point scale.

Two reviewers assessed the quality of the trials.

Data extraction
Data were extracted on the proportions of patients with COPD exacerbations, severe exacerbations (requiring hospitalisation) and respiratory deaths (due to lower respiratory tract event) in order to calculate the relative risk (RR) with 95% confidence interval (CI). Trial investigators were contacted for additional information where necessary.

Two reviewers extracted the data and any differences were resolved by consensus.

Methods of synthesis
The RRs were pooled in a fixed-effect meta-analysis, owing to minimal heterogeneity found when applying the χ² test. The results were reported separately for placebo-controlled trials of anticholinergics and β₂-agonists, and for comparisons of anticholinergics and β₂-agonists. Further analysis was carried out on those trials that reported no respiratory death in order to calculate the absolute risk difference. The number-needed-to-treat (NNT) and number-
needed-to-harm (NNH) were also calculated. A sensitivity analysis was planned to take account of the quality assessment. Publication bias was reported to have been assessed by funnel plots.

**Results of the review**

Twenty-two trials (n=15,276 patients) were included in the review.

The drop-out rate was 18.5% in the anticholinergic group, 19% in the β₂-agonist group and 24.8% in the placebo group. Sensitivity analysis was not carried out since all the trials were judged to be of sufficiently good quality. There was no reported evidence of publication bias.

**Inhaled anticholinergics compared with placebo (7 trials).**

Statistically significant reductions in risk of withdrawal from the trial for COPD exacerbation and severe exacerbations were reported (respectively) as 40% (RR 0.60, 95% CI: 0.48, 0.75) and 33% (RR 0.67, 95% CI: 0.53, 0.86). The absolute risk reduction for severe exacerbations was approximately 4 cases per 100 patient-years of treatment (NNT=25). The risk of respiratory deaths was significantly reduced in the intervention group by 73% (RR 0.27, 95% CI: 0.09, 0.81). The absolute risk reduction was 0.36% per year (NNT=278).

**β₂-agonists compared with placebo (13 trials).**

Twelve trials assessed salmeterol and formoterol. In the intervention group, a statistically significant reduction in risk of withdrawal from the trial for COPD exacerbation was reported as 19% (RR 0.81, 95% CI: 0.68, 0.95), with no significant effect for hospitalisation. There was an associated increase in respiratory deaths (RR 2.47, 95% CI: 1.12, 5.45). The absolute risk increase was 0.76% per year (NNH=131).

**Anticholinergics compared with β₂-agonists (7 trials).**

β₂-agonists showed a statistically significant increase in COPD exacerbations that necessitated withdrawal from the trial (RR 2.02, 95% CI: 1.39, 2.93), and severe exacerbations requiring hospitalisation (RR 1.95, 95% CI: 1.06, 3.59). There was a non significant association between increased respiratory death and β₂-agonists in the 2 trials that assessed this outcome. There were no significant differences in severe exacerbations or death when combined anticholinergics and β₂-agonists were compared with anticholinergics alone (4 trials).

**Authors' conclusions**

Inhaled anticholinergics can significantly reduce the risk of severe exacerbations and respiratory deaths in COPD patients. β₂-agonists are associated with increased respiratory deaths.

**CRD commentary**

This review addressed a clear research question that was supported by adequately detailed inclusion criteria. The search strategy included relevant databases and attempts were made to minimise language bias. It is not clear whether unpublished material was sought, although publication bias was addressed in the analysis. The validity assessment criteria were appropriate for the included study design and the results of this were highlighted to demonstrate the reliability of the results. It is not clear how studies were selected for inclusion, but other aspects of the review process appeared to be carried out with sufficient rigour. The method of synthesis was appropriate, although (as the authors acknowledged) the number of studies was small in some analyses. This was a largely well-conducted review and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that anticholinergics should be the treatment of choice for patients with COPD.

**Research:** The authors stated that the long-term safety of β₂-agonists should be evaluated.

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Other publications of related interest
This additional published commentary may also be of interest.


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