Safety of long-acting beta-agonists in stable COPD: a systematic review

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CRD summary
The authors concluded that long-acting bronchodilators were beneficial in patients with stable moderate to severe COPD and did not increase the risk of respiratory death. The evidence also indicated that tiotropium was superior to LABAs. This was a generally well-conducted review. The authors’ conclusions appeared to reflect the evidence and was likely to be reliable.

Authors' objectives
To assess the safety and efficacy of long-acting bronchodilators – long-acting Beta 2-agonists (LABAs) – compared to placebo and anticholinergics in patients with chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Controlled Trials Register were searched for articles through to 2007 without language restrictions. Search terms were reported. In addition, references of included studies, reviews, and texts were searched manually. Trial abstracts were excluded.

Study selection
Randomised controlled studies (RCTs) with parallel group or cross-over designs were eligible for inclusion. These needed to compare inhaled LABAs (administered via metered-dose inhaler or dry powder) as monotherapy or in combination with inhaled corticosteroids (ICS) with placebo, or with inhaled ipratropium bromide or inhaled tiotropium with or without short-acting Beta 2-agonists (SABAs). The minimum time period was four weeks. Patients needed to be over the age of 35 years with stable COPD (diagnosed using certain criteria).

Eligible primary outcomes were: severe COPD exacerbations resulting in withdrawal or hospitalisation; all-cause mortality due to any cause; and respiratory mortality due to respiratory events. Secondary outcomes were mean change from baseline of post-bronchodilator FEV1, mean change from baseline in the St George Respiratory Questionnaire (SGRQ) and need for rescue bronchodilator.

Included RCTs were predominantly of men with a mean age of 63.3 years ± 10.3 years. Most studies included patients with concomitant use of ICS. Treatment groups used salmeterol or ipratropium at varying doses. Included studies reported at least one primary or secondary outcome.

Two reviewers independently screened studies for relevance, with any disagreements resolved by consensus.

Assessment of study quality
Studies were assessed for methodological quality according to criteria published by Jadad et al, with a score of 0 to 5 allocated to each study, with 5 denoting the highest quality. The authors did not state how the validity assessment was performed.

Data extraction
The authors did not explicitly state how data were extracted.

Methods of synthesis
A fixed-effect model (or random-effects model where there was evidence of heterogeneity) was used to pool relative risks (RRs) for dichotomous data. The weighted mean difference (WMD) and 95% confidence intervals were calculated for continuous data using the same unit of measure. Where no respiratory deaths were reported, absolute risk differences were calculated. Where pooled-effect estimates were significantly different, the number needed to treat (NNT) was calculated. Where possible, analyses were based on an intention-to-treat (ITT) basis. An interaction test was used to compare subgroup results according to study duration, reversibility to salbutamol (greater than 15 per cent reversibility of FEV1 after a small dose of SABA), use of different LABAs and concomitant use of ICS. Heterogeneity
was assessed using the Q statistic and $I^2$ test. Sensitivity analyses were conducted to compare results using the fixed-effect model against results using the random-effects model. The fail-safe N test was used to adjust for publication bias.

**Results of the review**
Twenty seven RCTs (n=20,527) were included in the review. RCTs scored between 3 and 5 on the Jadad scale, with five studies scoring 5.

Significantly fewer incidences of severe COPD exacerbations were reported in patients receiving LABA compared to placebo. RR reduction was 0.78 (95% CI: 0.67, 0.91, $p<0.001$, $I^2=0\%$) (14 RCTs). The NNT was 30 (95% CI: 20, 52).

RCTs reporting one or more deaths reported no significant differences between patients in the LABA and placebo groups for all-cause mortality (nine of 13 RCTs) or respiratory deaths (five of 12 RCTs). Subgroup analyses (two RCTs) showed significant reductions in respiratory deaths in patients receiving LABA combined with ICS compared to LABA monotherapy; RR 0.35 (95% CI: 0.14, 0.93, $p=0.03$, $I^2=0\%$).

Significant benefits in airflow limitation measures, health-related quality of life, and use of rescue medication were reported in patients receiving LABAs. However, there was significant heterogeneity among studies reporting the two former outcomes ($I^2=92\%$ and $I^2=83\%$, respectively). Fewer incidences of severe COPD exacerbations were reported in patients receiving tiotropium compared with patients receiving LABAs (three RCTs); RR 0.52 (95% CI: 0.31, 0.87). Again, there was evidence of significant heterogeneity ($I^2=57.6\%$).

ARRs and adjustments for publication bias were reported in the review.

**Authors' conclusions**
The evidence supported the suggestion that LABAs had beneficial effects in patients with stable moderate-to-severe COPD without increasing the risk of respiratory death. The evidence also indicated that tiotropium was superior to LABAs in the treatment of stable COPD.

**CRD commentary**
The reviews objectives and inclusion criteria were clear. A relevant literature search was conducted with attempts to reduce language and publication bias. Attempts were made to reduce reviewer error and bias for study selection. But, as the process was not made explicit for data extraction and validity assessment, bias cannot be ruled out. Studies were of acceptable quantity and quality, and had adequate sample sizes. Appropriate methods were used to synthesise the data and investigate heterogeneity, although evidence of significant heterogeneity in some comparisons was not investigated further. This was a generally well-conducted review. The authors' conclusions appeared to reflect the evidence and were likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that the beneficial effects of LABAs was evident in both poorly reversible and reversible patients with stable moderate-to-severe COPD. LABAs also suggested beneficial changes regarding lung function, quality of life and use of daily rescue medication with SABAs, but the clinical significance of the effects was unclear. Benefits on spirometric measure were greater in patients with reversibility to salbutamol. With the exception of health-related quality of life, salmeterol and formoterol reported equivalent effects. The effects of tiotropium on exacerbations and lung function appeared to be somewhat superior to LABAs.

Research: The authors did not state any implications for future research.

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