Long-acting beta2-agonists for maintenance therapy of stable chronic obstructive pulmonary disease: a systematic review

Shukla V K, Husereau D R, Boucher M, Mensinkai S, Dales R

Authors' objectives
To assess the efficacy and safety of long-acting beta2-agonists salmeterol and formoterol in comparison with placebo or anticholinergic agents, with or without the additional use of short-acting beta2-agonist agents, in patients with stable chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE, HealthSTAR, Biosis Previews, and the Cochrane Library were searched from inception to 2000/2001, with a PubMed update in January 2002 (the search terms were reported). Health Technology Assessment and related websites were also searched, as were conference abstracts of major respiratory associations and clinical trial registries. Handsearches of selected journals and the bibliographies of relevant papers were conducted and the relevant drug manufacturers were contacted. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs), both parallel and crossover, were eligible for inclusion.

Specific interventions included in the review
Studies comparing salmeterol or formoterol with placebo or an anticholinergic agent, with or without the additional use of short-acting beta2-agonists, were eligible for inclusion. Only studies where the duration of therapy was at least 4 weeks were eligible. The included studies compared salmeterol and placebo; salmeterol, ipratropium bromide and placebo; formoterol, theophylline and placebo; and formoterol, ipratropium bromide and placebo. The duration of treatment in the included studies ranged from 4 weeks to 12 months. The drug doses ranged from 42 to 100 microg twice daily (b.i.d.) for salmeterol, from 12 to 24 microg b.i.d. for formoterol, and from 36 microg four times daily to 80 microg three times daily for ipratropium bromide.

Participants included in the review
Studies of non-asthmatic participants with stable COPD, an FEV1 (forced expiratory volume in 1 second) of 75% or less than predicted, an FEV1/FVC (forced vital capacity) ratio less than 70% predicted, and less than 15% improvement in FEV1 after a dose of a short- or long-acting beta2-agonist, were eligible for inclusion. Stable COPD was defined as no recent infections, exacerbations or hospitalisation in the previous month.

Outcomes assessed in the review
Studies assessing the following outcomes were eligible for inclusion: lung function; 6-minute walk test and/or shuttle walking test; health-related quality of life; dyspnea measurement; number of exacerbations; rescue use of a short-acting beta2-agonist (salbutamol); and incidences of tachycardia, hypokalaemia and dry mouth.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the identified articles. Any disagreements were resolved by consensus, or by recourse to a third-party if necessary.

Assessment of study quality
The studies were assessed, using a published scale, for appropriateness of randomisation, double-blinding, withdrawals and drop-outs. The studies were also assessed for allocation concealment. Two reviewers independently assessed each study. Any disagreements were resolved by consensus, or by recourse to a third-party if necessary.
Data extraction
The data extraction was carried out in duplicate. Any disagreements were resolved by consensus, or by recourse to a third reviewer. Where the outcome data were only available graphically, both reviewers independently estimated the value of the outcome from the graph and the mean of the two estimated values was used. Mean differences and 95% confidence intervals were estimated for continuous outcomes, and odds ratios and 95% confidence intervals for binary outcomes. When intention-to-treat data were unavailable, end point data for participants completing the trial were used.

Methods of synthesis
How were the studies combined?
A narrative synthesis of the studies was undertaken.

How were differences between studies investigated?
Between-study differences could be evaluated through the text and tables provided.

Results of the review
Nine reports of 8 unique RCTs were included (n=1,736). Five were of a parallel-group design and 3 were crossover trials.

Six of the trials were assessed as being of moderate quality and two of low quality.

Salmeterol.
When compared with placebo, salmeterol improved night-time and day-time dyspnea and FEV1, reduced the use of short-acting beta2-agonists as rescue therapy, and improved disease-specific quality of life. Salmeterol did not show any improvement over placebo on the 6-minute walk test. There was no significant improvement in the FEV1 or transition dyspnea index when salmeterol was compared with ipratropium bromide.

Formoterol.
When compared with placebo, formoterol reduced the severity of patient-assessed morning and evening dyspnea and FEV1. Formoterol did not show any improvement over placebo on the 6-minute walk test or for quality of life. There were no significant improvements in any of the outcome measures, except peak expiratory flow rate, when formoterol was compared with ipratropium bromide.

Relevant safety data were not available from the trials.

Authors' conclusions
The authors concluded that although salmeterol and formoterol were superior to placebo in decreasing the use of rescue inhalers, they did not improve functional outcomes such as the distance travelled in a 6-minute walk test. Compared with ipratropium bromide, neither salmeterol nor formoterol were more efficacious.

CRD commentary
The review question was clearly defined in terms of the intervention, participants, the outcomes of interest and study design. A range of relevant databases was searched and the subject headings were provided. Unpublished data were sought and no language restrictions were applied. The study selection, data extraction and quality assessment processes were carried out in duplicate, which helps to reduce errors and bias. Sufficient details of the individual studies appear to have been provided. The authors carried out a narrative synthesis rather than a meta-analysis due to the clinical heterogeneity of the included studies. A quality assessment was carried out and the review findings were discussed in the context of study quality. The authors' conclusions appear to be supported from the data presented.

The authors discussed how their findings compared with the conclusions of an earlier Cochrane review.
Implications of the review for practice and research
The authors did not state any implications for further research and practice.

Bibliographic details

Other publications of related interest

Indexing Status
Subject indexing assigned by CRD

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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.