Comparison of tiotropium plus formoterol to tiotropium alone in stable chronic obstructive pulmonary disease: a meta-analysis


CRD summary
This review found that tiotropium plus formoterol significantly improved lung function and symptom scores compared with tiotropium alone in patients with stable chronic obstructive pulmonary disease. The authors recommended further research to establish long-term efficacy and safety of the combination. The conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To compare the efficacy and safety of tiotropium plus formoterol with that of tiotropium alone in patients with stable chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2010. Search terms were reported. There were no language restrictions. Reference lists of primary publications and review articles were searched.

Study selection
Randomised controlled trials (RCTs) that compared tiotropium plus formoterol or arformoterol with tiotropium alone in patients with stable COPD (American Thoracic Society/European Respiratory Society criteria) were eligible for inclusion. Trials could be parallel group or crossover. Minimum duration of treatment was two weeks. Outcomes of interest were change in average and trough forced expiratory volume (FEV₁) and forced vital capacity (FVC) from baseline, COPD exacerbations, adverse events and transitional dyspnoea index (TDI).

Most included trials recruited participants with moderate to severe COPD (GOLD stages II to III). Patients with a prior history of asthma were excluded from most trials. The additional therapy assessed in most trials was inhaled powder formoterol; other additional therapies assessed were nebulised formoterol and nebulised arformoterol. Permitted co-therapies included short-acting beta₂-agonists and inhaled corticosteroids in most trials. Treatment duration ranged from two to 24 weeks.

Two independent reviewers selected studies for the review.

Assessment of study quality
Methodological quality was assessed using Cochrane Collaboration risk of bias criteria for adequate sequence generation, allocation concealment, blinding, absence of selective outcome reporting and missing/incomplete data addressed.

It appeared that quality was assessed by two independent reviewers.

Data extraction
Data were extracted to calculate odds ratios (ORs) for binary outcomes and mean differences for continuous outcomes, with associated 95% confidence intervals (CIs). Data were extracted by two independent reviewers. Study authors were contacted to obtain missing data.

Methods of synthesis
Trials were pooled by meta-analysis using fixed-effect models. Statistical heterogeneity was assessed using the Breslow-Day test (p<0.1 statistically significant). Random-effects models were used where heterogeneity was identified. $I^2$ was calculated (<25%, 25 to 75% and >75% represented low, moderate and high degrees of inconsistency). Publication bias was assessed by examination of funnel plots and Egger’s weighted regression test.
Results of the review
Eight RCTs (1,868 randomised participants) were included in the review. All trials used adequate sequence generation, addressed incomplete outcome data and were free of selective reporting. Six trials used blinding and reported allocation concealment.

Treatment with tiotropium plus formoterol was associated with significantly greater improvements from baseline in average FEV$_1$ (WMD 105mL, 95% CI 69 to 142; three trials), average FVC (WMD 135mL, 95% CI 96 to 174; two trials) and trough FEV$_1$ (WMD 53mL, 95% CI 30 to 76; four trials) compared with tiotropium alone. There was no significant difference for trough FVC. Mean change in TDI was significantly greater with tiotropium plus formoterol than with formoterol alone (WMD 1.50, 95% CI 1.01 to 1.99; two trials). Patients treated with the two drugs were significantly more likely to achieve a clinically significant change in TDI (OR 2.34, 95% CI 1.58 to 3.46; three trials). Heterogeneity was significant only for change in average FEV$_1$. Adverse events and COPD exacerbations did not differ significantly between groups.

Funnel plots and Egger's test did not suggest publication bias.

Authors' conclusions
Tiotropium plus formoterol significantly improved lung function and symptom scores compared with tiotropium alone.

CRD commentary
The review question and inclusion criteria were clear. The search covered a range of relevant sources without language restrictions. The authors did not search for unpublished studies; publication bias was assessed and no evidence of bias was found. Study selection, validity assessment and data extraction were done by two reviewers independently, which minimised risks of errors and bias. Quality of included trials was assessed using appropriate criteria for RCTs. Trials were pooled by meta-analysis. Standard methods were used to assess heterogeneity. Results for most outcomes were based on four or fewer of the eight included RCTs, which reduced the strength of the evidence base.

The authors' conclusions reflect the evidence presented and appear reliable. The implications for further research seemed appropriate in view of the relatively small number of participants and short duration of the included trials.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice

Research: The authors stated that larger and longer double-blind multicentre RCTs were required to confirm the efficacy and assess the safety of combined treatment with tiotropium and formoterol.

Funding
Clinical Speciality Key Program for Hospitals Affiliated to the Ministry of Health of China; Chinese Medical Association Clinical Medicine Chronic Respiratory Tract Diseases Scientific Research Special Fund.

Bibliographic details

PubMedID
21138499

DOI
10.1111/j.1440-1843.2010.01912.x

Original Paper URL

Indexing Status
Subject indexing assigned by NLM
AccessionNumber
12011001447

Date bibliographic record published
18/05/2011

Date abstract record published
27/07/2011

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.