Triple therapy for the management of COPD: a review

CRD summary
This review concluded that compared with long-acting anti-cholinergic bronchodilator monotherapy, triple therapy decreased the hospitalisation rate due to severe/acute exacerbations for the management of chronic obstructive pulmonary disease. These conclusions should be interpreted with caution given a lack of details on study quality and limitations in the review methods.

Authors' objectives
To compare the efficacy of triple therapy versus dual bronchodilator therapy (long-acting anti-cholinergic bronchodilator plus long-acting beta-agonist bronchodilator) or long-acting anti-cholinergic bronchodilator monotherapy for the management of chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE, CINAHL, PubMed (non-MEDLINE records only), Web of Science, BIOSIS Previews, Cochrane Database of Systematic Reviews, DARE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register and HTA Database were searched up to May 2009. Search terms were reported. Searches were updated up to October 2009.

Study selection
Randomised controlled trials (RCT), controlled clinical trials and cohort studies that evaluated triple therapy (long-acting anti-cholinergic bronchodilator, long-acting beta-agonist bronchodilator and an inhaled corticosteroid) versus dual bronchodilator therapy (long-acting anti-cholinergic bronchodilator plus long-acting beta-agonist bronchodilator; long-acting beta-agonist bronchodilator plus inhaled corticosteroid) or long-acting anticholinergic bronchodilator alone in patients with moderate to severe COPD were eligible for inclusion. The outcomes of interest were change in forced expiratory volume in the first second of expiration (FEVi), quality of life and incidence of exacerbations, hospitalisations, deaths and dyspnoea.

In the included studies, triple therapies involved tiotropium in combination with fluticasone/salmeterol or budesonide/formoterol. These studies used tiotropium alone as long-acting anti-cholinergic bronchodilator monotherapy. All included studies permitted concomitant therapies such as albuterol, terbutaline, salbutamol and theophylline. Study duration ranged from three months to 12 months. Baseline FEVi ranged from 25% to 70%. Where reported, patient age ranged from at least 35 years to at least 50 years. Quality of life was measured using the St George's Respiratory Questionnaire. Different instruments were used to measure dyspnoea.

Two reviewers independently assessed studies for inclusion. Any disagreements were resolved by consensus.

Assessment of study quality
Study quality was assessed using the Jadad scale of randomisation, blinding, withdrawals and drop-outs) with an additional criterion of allocation concealment.

The authors did not state how many reviewers performed quality assessment.

Data extraction
For continuous variables, data were extracted on mean and standard deviation to enable calculation of mean differences (MDs) and 95% confidence intervals (CIs). For dichotomous variables, data were extracted on event rates to enable calculation of relative risks (RRs) with 95% CIs.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Where appropriate, studies were combined in a meta-analysis; otherwise studies were combined in a narrative synthesis.
Pooled relative risks and weighted mean differences (WMDs), with 95% CIs, were calculated using a random-effects model. Statistical heterogeneity was assessed using the $I^2$ statistic.

**Results of the review**

Four trials were included in the review (1,287 participants). None of the trials reported a comparison between triple therapy and dual bronchodilator therapy (long-acting anticholinergic bronchodilator plus long-acting beta-agonist bronchodilator).

Compared to long-acting anti-cholinergic bronchodilator monotherapy, triple therapy was associated with a marginal significance for improvement in lung function as measured by FEVi (WMD 0.05L, 95% CI 0.00 to 0.11; three trials) and a significant improvement in quality of life (WMD 3.75, 95% CI 1.56 to 5.94; two trials). No substantial heterogeneity was found in these outcomes.

There were no significant differences in the rate of severe/acute exacerbations and mortality between the two groups. Substantial heterogeneity was only found in the outcome of severe/acute exacerbations ($I^2=93\%$).

Hospitalisation rates due to COPD exacerbations (two trials) were reduced significantly with triple therapy compared to long-acting anti-cholinergic bronchodilator monotherapy (RR 0.53, 95% CI 0.33 to 0.86 and 0.35, 95% CI 0.16 to 0.78). One trial reported a significant improvement in breathlessness using the triple therapy compared with monotherapy. Two trials did not find a significant difference in dyspnoea between the two groups.

**Authors’ conclusions**

Triple therapy decreased the hospitalisation rate due to severe/acute COPD exacerbations compared with long-acting anti-cholinergic bronchodilator monotherapy.

**CRD commentary**

This review’s inclusion criteria were clear. Several relevant databases were searched. Efforts were made to find both published and unpublished studies, which minimised the risk of publication bias. The authors did not state whether any language restrictions were applied in the search and this made it difficult to assess the risk of language bias. Attempts were made to minimise reviewer errors and biases during study selection; it was unclear whether data extraction and quality assessment were also performed in duplicate. Appropriate criteria were used to assess study quality. The authors discussed some aspects of study quality but full details were not reported. Statistical heterogeneity was assessed. Use of a random-effects model to pool the results from the small number of trials may not have been appropriate (there were insufficient data for the model to calculate between-study variance).

The authors’ conclusions should be interpreted with caution given the lack of details on study quality and limitations in the review methods.

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

**Practice:** The authors did not state any implication for practice.

**Research:** The authors stated that more evidence was required to determine the efficacy of triple therapy compared with current management strategies for the management of chronic obstructive pulmonary disease.

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