Tiotropium for treatment of stable COPD: a meta-analysis of clinically relevant outcomes
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CRD summary
The review found that, compared with placebo or ipratropium, tiotropium improved the quality of life, eased difficulties with breathing, and reduced exacerbations and related hospitalisations in patients with stable chronic obstructive pulmonary disease. The authors' conclusions reflect the evidence base, but because of potential publication and language bias, the conclusions should be considered tentative.

Authors' objectives
To assess the effectiveness of tiotropium versus placebo, ipratropium and long-acting beta-2 agonists on clinically relevant outcomes in patients with chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE, CINAHL, AMED, Web of Knowledge and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1990 to January 2010 for studies published in English; search terms were reported. Reference lists of retrieved studies were reviewed. The pharmaceutical company Boehringer Ingelheim was contacted for unpublished data and to investigate the overlap between studies.

Study selection
Parallel-group or crossover randomised controlled trials (RCTs) of adult patients (40 years or older) with stable COPD (as consistent with American Thoracic Society/European Respiratory Society or Global Initiative for Chronic Obstructive Lung Disease or GOLD diagnostic criteria), with follow-up of 12 weeks or more after randomisation, were eligible for the review. Eligible patients should not have had an exacerbation in the previous four weeks. Trials were required to compare tiotropium with placebo, ipratropium bromide or long-acting beta agonists (salmeterol or formoterol).

Eligible outcomes were COPD exacerbations (as defined in the paper), related hospitalisations, health-related quality of life, dyspnoea (difficulty in breathing), and adverse events.

In the included trials, patients had stable moderate to severe COPD according to the GOLD criteria. Included patients had a mean age 65 year, 77% were men and 33% were current smokers (where reported). Mean duration of COPD was nine years. Tiotropium was compared with placebo, ipratropium, salmeterol, formoterol and a combination of tiotropium and formoterol. In most trials, the dose of tiotropium was 18μg daily. Co-therapies such as salbutamol and steroids were permitted.

Two reviewers independently selected studies for the review, with disagreements resolved by discussion with a third reviewer.

Assessment of study quality
Trials were assessed for quality using the Jadad scale; criteria included randomisation, blinding and reporting of withdrawals and drop-outs. Trials with a score of under 3 points was considered of poor quality.

Two reviewers independently performed validity assessment, with disagreements resolved by discussion with a third reviewer.

Data extraction
Data were extracted on the incidence of the outcomes; odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Clinically relevant changes in health-related quality of life were defined as a difference in 4 points on the St George's Respiratory Questionnaire. Changes in dyspnoea were defined as a difference of 1 point in the Transition Dyspnoea Index.

Two reviewers independently extracted data according to a standardised protocol, with disagreements resolved by...
discussion with a third reviewer.

Methods of synthesis
Trials were pooled in meta-analyses. Summary odds ratios with 95% confidence intervals were calculated, using a fixed-effect model. Heterogeneity was quantified by the I² value. When moderate heterogeneity was found (I² over than 25%), a random-effects model was used. Sensitivity analysis was undertaken according to duration of follow-up (12 to 52 weeks versus over 52 weeks).

Results of the review
Sixteen RCTs (n=16,301 patients) were included in the review. Trials had Jadad scores that ranged from 3 to 5 points, which indicated adequate quality. Follow-up ranged from 12 to 208 weeks.

Health-related quality of life (seven RCTs): Tiotropium was associated with a significantly greater and clinically important change in quality of life when compared with placebo (OR 1.61, 95% CI 1.38 to 1.88; I²=41.6%; six RCTs) or ipratropium (OR 2.03, 95% CI 1.34 to 3.07; one RCT) in patients with chronic obstructive pulmonary disease (COPD). There was no evidence of a significant difference in quality of life in one study when tiotropium was compared to salmeterol.

Dyspnoea: Tiotropium was associated with a significantly greater and clinically important reduction in dyspnoea when compared with placebo (OR 1.96, 95% CI 1.58 to 2.44; I²=0%; two RCTs) or ipratropium (OR 2.10, 95% CI 1.28 to 3.44; number of RCTs not reported). There was no evidence of a significant difference in the incidence of dyspnoea when tiotropium was compared with salmeterol.

COPD exacerbations (13 RCTs): Tiotropium was associated with a significant reduction in the rate of COPD exacerbations when compared with placebo (OR 0.83, 95% CI 0.72 to 0.94; I²=49.7%; 11 RCTs) or ipratropium (OR 0.64, 95% CI 0.44 to 0.92; one RCT). There was no evidence of a significant difference in the rate of COPD exacerbations in two RCTs when tiotropium was compared with salmeterol.

COPD exacerbation-related hospitalisation (nine studies): Tiotropium was associated with significantly fewer hospitalisations when compared with placebo (OR 0.89, 95% CI 0.80 to 0.98; I²=18.2%; seven RCTs). A similar but non significant reduction was found when tiotropium was compared with salmeterol (OR 0.54, 95% CI 0.29 to 1.00; I²=0%; two RCTs). There was no evidence of a significant association when tiotropium was compared with ipratropium (one RCT) or formoterol (one RCT).

Adverse events: Tiotropium was associated with a greater incidence of dry mouth when compared with placebo (OR 3.19, 95% CI 1.79 to 5.70; I²=59%; eight RCTs), salmeterol (OR 4.60, 95% CI 2.37 to 8.93; I²=0%; two RCTs) or ipratropium (OR 3.09, 95% CI 1.68 to 5.66; I²=0%; two RCTs). Compared with salmeterol, tiotropium was associated with a statistically significant lower risk of a serious adverse event (OR 0.39, 95% CI 0.16 to 0.95; one RCT), but there was no evidence of significant differences in the incidence of serious adverse events in seven RCTs where tiotropium was compared with placebo.

Sensitivity analysis, with the removal of longer term trials (over one year) indicated that significant differences between tiotropium and placebo in health-related quality of life, COPD exacerbations and hospitalisations. The rate of serious adverse events remained non significant.

Authors’ conclusions
Tiotropium showed superior efficacy to placebo or ipratropium, with improved quality of life and dyspnoea and reduced exacerbations and related hospitalisations in patients with stable COPD.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared appropriate. Several relevant sources were searched to identify studies; attempts were made to find unpublished studies. Studies were restricted to those written in English, so language bias could not be ruled out. The authors acknowledged that they may have missed unpublished studies in spite of a systematic search strategy, so publication bias could not be excluded. Appropriate methods were used to select studies, perform data extraction and appraise trials for quality, which meant that reviewer error and bias were unlikely.
A standardised tool was used to appraise trial quality. None of the included trials were considered to be of poor quality. However, the included trials had different criteria for the use of co-medications, which may have introduced some confounding. Trials were appropriately pooled in meta-analyses. Heterogeneity was found in some analyses; where this occurred, the results were reported using a random-effects model. Trial duration varied widely, but sensitivity analysis was undertaken to test the robustness of findings according to duration of follow-up; overall results were mostly confirmed with restriction to shorter term (under one year) trials. Results that compared tiotropium with placebo were based on multiple trials, but comparisons of tiotropium with ipratropium or long-acting beta agonists were mostly based on only one or two trials, which gave less precise findings in some cases.

The authors' conclusions reflect the evidence base, but because of potential publication and language bias, the conclusions should be considered tentative.

Implications of the review for practice and research
Practice: The authors stated that tiotropium should be considered for first-line therapy and the maintenance of COPD.

Research: The authors stated that the number of hospitalisations per patient per year should be studied in future reviews. They stated that further research was needed to compare the efficacy of tiotropium against other COPD treatments, especially those added to a long-acting beta agonist treatment.

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