Tiotropium for the treatment of stable chronic obstructive pulmonary disease: a systematic review with meta-analysis
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CRD summary
This review concluded that the use of tiotropium was beneficial in treatment of patients with moderate-to-severe stable chronic obstructive pulmonary disease. Previous evidence in favour of the superiority of tiotropium over long-acting beta-agonists was also supported. As the results may not be generalisable and potential bias was possible, these conclusions may not be reliable.

Authors' objectives
To update the evidence of the effectiveness of tiotropium bromide for the treatment of stable chronic obstructive pulmonary disease patients.

Searching
Searches were performed in MEDLINE (1966-2006), EMBASE (1974-2006), CINAHL (1982 - 2006) and the Cochrane Central Register of Controlled Trials (first quarter 2006). Search terms were reported. Reference lists of included studies, texts and reviews and were also searched. The top 20 respiratory journals were handsearched. Boehringer Ingelheim was contacted to identify additional published and unpublished trials. There were no language restrictions.

Study selection
Parallel or crossover randomised controlled trials (RCTs) comparing inhaled tiotropium bromide with placebo, inhaled ipratropium bromide or inhaled long-acting beta-agonists in patients aged over 35 years with stable chronic obstructive pulmonary disease (COPD) were eligible for inclusion. Stable chronic obstructive pulmonary disease had to satisfy the American Thoracic Society (ATS), European Respiratory Society (ERS) or GOLD diagnostic criteria. Included trials had to be longer than a week; studies on acute effects (less than a week) were excluded. The primary outcomes were chronic obstructive pulmonary disease exacerbations, hospitalisations and mortality. Secondary outcomes were health status, symptoms, spirometric measures, static lung volumes, exercise performance, inhaled rescue medication and side-effects.

The mean age of the included patients ranged from 57.6 to 67.8 years, 56.0 to 98.5% were male. Some patients were current or past smokers. Included patients exhibited stable chronic obstructive pulmonary disease that met GOLD criteria stages II and III, with duration ranging between 7.5 and 12 years. The majority of the trials were randomised, double blinded parallel group trials of 18mcg tiotropium, ranging from 1 week to 12 months in duration.

Studies were selected independently by two reviewers and disagreements resolved by consensus.

Assessment of study quality
Methodological quality of the trials was determined using the Jadad scale to give a score out of 5. Adequacy of randomisation, blinding and the handling of withdrawals and drop-outs was assessed.

It was unclear but appeared that validity was assessed independently by two reviewers.

Data extraction
It was unclear but appeared that two reviewers independently extracted the data.

Methods of synthesis
Data were pooled as odds ratios for binary outcomes and weighted mean difference for continuous outcomes with corresponding 95% confidence intervals (CIs). For continuous outcomes, standardised mean difference was calculated,
if variables used different units of measure. These were pooled in fixed-effects meta-analysis. The number needed to treat to prevent the adverse outcome of interest was also calculated. Statistical heterogeneity was assessed using the DerSimonian and Laird $Q$ statistic and the $I^2$ test. Subgroup analyses (which included baseline severity, co-therapies, length of treatment and methodological quality) and sensitivity analyses were performed to explain heterogeneity found.

**Results of the review**

Thirteen RCTs were included (n=6,078). The trial quality Jadad score ranged from 2 to 5. The majority of trials had a quality score of 3. Sample sizes ranged from 31 to 1,829 patients.

**Tiotropium versus placebo:**

Tiotropium significantly reduced chronic obstructive pulmonary disease exacerbations compared to placebo (odds ratio 0.76, 95% CI: 0.66, 0.87, p=0.0001, number needed to treat 21, 95% CI: 13, 50, eight trials). Hospital admissions were significantly reduced with tiotropium compared to placebo (odds ratio 0.59, 95% CI: 0.47, 0.73, p=0.0001, number needed to treat 20, 95% CI: 14, 34, three trials). The difference in all-cause mortality between tiotropium and placebo groups (four trials) was not statistically significant and there was no significant statistical heterogeneity detected for these outcomes.

**Tiotropium versus ipratropium:**

Primary outcome data were not available. Tiotropium significantly improved mean change in trough FEV1 (forced expiratory outflow in the first second) and FVC (forced vital capacity) from baseline compared with ipratropium (two trials); tiotropium with a weighted mean difference of 0.15L (95% CI: 0.11, 0.18, p=0.0001); and ipratropium with a weighted mean difference of 0.22L (95% CI: 0.31, 0.31, p=0.0001). The mean change in peak FEV1 and FVC were also increased in the tiotropium group compared to ipratropium: tiotropium with a weighted mean difference of 0.10 (95% CI: 0.06, 0.14, p=0.0001); and ipratropium with a weighted mean difference of 0.09 (95% CI: 0.01, 0.08, p=0.05). No significant heterogeneity was detected.

**Tiotropium versus long-acting beta-agonists:**

Hospital admissions were significantly reduced in the tiotropium group compared with salmeterol (odds ratio 0.67, 95% CI: 0.46, 0.98, p=0.04, number needed to treat 33, 95% CI: 17, 1007, n=1,460 patients). No heterogeneity was detected. There was no significant difference in chronic obstructive pulmonary disease exacerbations with tiotropium compared with long-acting beta-agonists. There was evidence of heterogeneity between studies ($I^2=55.6\%$). Sensitivity analyses showed that statistical heterogeneity was due to methodological quality.

Further analyses were reported.

**Authors' conclusions**

The use of tiotropium had beneficial effects in stable moderate-to-severe chronic obstructive pulmonary disease patients and increased the evidence in favour of the superiority of tiotropium over long-acting beta-agonists.

**CRD commentary**

This research question was well defined and the inclusion criteria were clear with regard to participants, intervention, outcomes and study design. The authors searched for published and unpublished studies with no language restrictions, reducing the possibility of publication and language bias. Study selection was performed independently by two reviewers reducing the possibility of reviewer bias and error. However, the processes by which data were extracted and validity was assessed were not clearly reported, so although it appeared that similar steps were taken, it was not certain. Validity of the primary studies was assessed appropriately. The clinical characteristics of the study population were quite similar. Statistical heterogeneity also assessed and investigated where present. There may be issues regarding generalisability, as the majority of patients were male. Also, patients were double counted, which increased the sample size and might have biased the results. Due to the potential for bias, the authors' conclusions may not be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that as chronic obstructive pulmonary disease-related exacerbations and hospitalisations are a contributor to the cost of chronic obstructive pulmonary disease, tiotropium may have the potential to reduce the economic burden of this disease.

Research: The authors stated that larger and more definitive controlled studies assessing the additive effect of tiotropium and long-acting beta-agonists on chronic obstructive pulmonary disease are needed. Also, the use of inhaled corticosteroids along with tiotropium and long-acting beta-agonists requires evaluation.

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