The efficacy and safety of tiotropium in Chinese patients with stable chronic obstructive pulmonary disease: a meta-analysis

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CRD summary
The review found that among Chinese people with stable chronic obstructive pulmonary disease, tiotropium improved pulmonary function and symptoms, reduced exacerbations and was safe. The authors' conclusions appear reliable.

Authors' objectives
To evaluate the safety and efficacy of tiotropium for Chinese people with stable chronic obstructive pulmonary disease (COPD).

Searching
The Cochrane Library, ClinicalTrials.gov, MEDLINE, EMBASE and major Chinese databases (including 11 listed in the review) were searched for studies published between 2002 and July 2008. Search terms were reported. The search was not restricted by language. Studies that were unpublished or available only as abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) that compared tiotropium to placebo or ipratropium in Chinese people with stable COPD (defined using published diagnostic criteria) who had no evidence of an exacerbation in the month preceding the trial were eligible for inclusion. Trials needed to be at least four weeks in duration and report data on efficacy or safety. The review reported pulmonary function measures (for example, peak FEV₁, FEV₁ %) as a primary outcome. Secondary outcomes included symptoms, exacerbations, tolerability and safety.

Included studies restricted participation to people with an FEV₁/FVC ratio (forced expiratory volume in one second/forced vital capacity) of 0.70 or less. Most studies required that FEV₁ % be at least 30% of the predicted value. In all studies, 18μg of tiotropium was given once daily. Control groups received either ipratropium 20μgs four times daily or placebo. Duration of follow-up ranged from four to 12 weeks.

Two reviewers independently selected studies for inclusion. Differences were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed study quality using criteria adapted from three existing checklists. Criteria included randomisation, allocation concealment, blinding, follow-up, methods of analysis, withdrawals and results. Full details of the criteria assessed were not provided. Summary scores based on the Jadad scale were reported.

Data extraction
Two reviewers independently extracted the data. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes and mean differences for continuous outcomes. Intention-to-treat data were used when available.

Methods of synthesis
Studies were combined using a fixed-effect model to calculate pooled risk ratios and weighted mean differences (WMDs) with 95% CIs. Numbers needed to treat (NNT) and harm (NNH) were also calculated from the summary risk ratios. Statistical heterogeneity was assessed using the Q statistic and the I² statistic. It was planned to use a random-effects model in the event of statistical heterogeneity. Studies were initially grouped by comparison (placebo or ipratropium), but in the absence of heterogeneity studies were pooled across comparisons. Publication bias was assessed using funnel plots and modified Macaskill’s test. Sensitivity analyses were conducted to investigate the effects of random-effects analysis, study quality, duration and sample size.

Results of the review
Eleven RCTs were included in the review (n=1,006, range 40 to 221). Five RCTs scored 5 points out of five for validity, two scored 4 points, four scored 3 points and one scored 2 points. Ten studies were double-blinded.

**Pulmonary function**: When tiotropium was compared with either placebo or ipratropium, there was a significantly greater improvement in the tiotropium group for both FEV$_1$ (WMD 304mL, 95% CI 271 to 337; six RCTs) and FEV$_1$% (WMD 8.35%, 95% CI 5.40 to 11.31; four RCTs).

**Other outcomes**: When tiotropium was compared with either placebo or ipratropium, the rate of symptom improvement was significantly higher in the tiotropium group (RR 2.0, 95% CI 1.61 to 2.49, NNT=6, 95% CI 5 to 9; four RCTs). When tiotropium was compared with placebo, the rate of COPD exacerbation was significantly reduced in the tiotropium group (RR 0.07, 95% CI: 0.01 to 0.54; two RCTs). There was no statistically significant difference in the rate of COPD exacerbation between tiotropium and ipratropium (one RCT). There was no significant difference in the risk of adverse events in the tiotropium group compared with placebo. Adverse event rates were comparable when tiotropium was compared with ipratropium (six RCTs).

No significant statistical heterogeneity was found for any of the above analyses ($I^2=0\%$). There was no clear evidence of publication bias. Sensitivity and subgroup analyses did not materially affect any of the results.

**Authors' conclusions**
Among Chinese people with stable chronic obstructive pulmonary disease, tiotropium improved pulmonary function and symptoms, reduced exacerbations and was safe.

**CRD commentary**
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies without language restriction. Exclusion of unpublished studies meant that the review was prone to publication bias, but formal assessment revealed no such bias. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer select studies, conduct validity assessment and extract data. The criteria used to assess study validity were not clearly described and few details were reported about the quality of individual studies (such as method of allocation concealment, drop-out rates). Appropriate statistical techniques were used to combine the data and assess for statistical heterogeneity. The authors' conclusions appear reliable.

**Implications of the review for practice and research**
**Practice**: The authors stated that tiotropium appeared to be a reasonable first-line choice for Chinese people with stable chronic obstructive pulmonary disease.

**Research**: The authors stated that more long-term RCTs were needed to determine the efficacy and safety of tiotropium.

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