# Tiotropium versus placebo for chronic obstructive pulmonary disease (Review)

**Karner C, Chong J, Poole P**

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Charlotta Karner[1], Jimmy Chong[2], Phillippa Poole[3]

[1]BMJ-TAG, BMJ, London, UK. [2]Tauranga Hospital, Tauranga, New Zealand. [3]Department of Medicine, University of Auckland, Auckland, New Zealand

Contact address: Charlotta Karner, BMJ-TAG, BMJ, Tavistock Square, London, WC1H 9JR, UK. ckarner@bmj.com.

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## ABSTRACT

### Background

Tiotropium is an anticholinergic agent which has gained widespread acceptance as a once daily maintenance therapy for symptoms and exacerbations of stable chronic obstructive pulmonary disease (COPD). In the past few years there have been several systematic reviews of the efficacy of tiotropium, however, several new trials have compared tiotropium treatment with placebo, including those of a soft mist inhaler, making an update necessary.

### Objectives

To evaluate data from randomised controlled trials (RCTs) comparing the efficacy of tiotropium and placebo in patients with COPD, upon clinically important endpoints.

### Search methods

We searched the Cochrane Airways Group's Specialised Register of Trials (CAGR) and ClinicalTrials.gov up to February 2012.

### Selection criteria

We included parallel group RCTs of three months or longer comparing treatment with tiotropium against placebo for patients with COPD.

### Data collection and analysis

Two review authors independently assessed studies for inclusion and then extracted data on study quality and the outcome results. We contacted study authors and trial sponsors for additional information, and collected information on adverse effects from all trials. We analysed the data using Cochrane Review Manager 5, RevMan 5.2.

### Main results

This review included 22 studies of good methodological quality that had enrolled 23,309 participants with COPD. The studies used similar designs, however, the duration varied from three months to four years. In 19 of the studies, 18 mcg tiotropium once daily via the Handihaler dry powder inhaler was evaluated, and in three studies, 5 or 10 mcg tiotropium once daily via the Respimat soft mist inhaler was evaluated. Compared to placebo, tiotropium treatment significantly improved the mean quality of life (mean difference (MD) -2.89; 95% confidence interval (CI) -3.35 to -2.44), increased the number of participants with a clinically significant improvement

(odds ratio (OR) 1.52; 95% CI 1.38 to 1.68), and reduced the number of participants with a clinically significant deterioration (OR 0.65; 95% CI 0.59 to 0.72) in quality of life (measured by the St George's Respiratory Questionnaire (SGRQ)). Tiotropium treatment significantly reduced the number of participants suffering from exacerbations (OR 0.78; 95% CI 0.70 to 0.87). This corresponds to a need to treat 16 patients (95% CI 10 to 36) with tiotropium for a year in order to avoid one additional patient suffering exacerbations, based on the average placebo event rate of 44% from one-year studies. Tiotropium treatment led to fewer hospitalisations due to exacerbations (OR 0.85; 95% CI 0.72 to 1.00), but there was no statistically significant difference in all-cause hospitalisations (OR 1.00; 95% CI 0.88 to 1.13) or non-fatal serious adverse events (OR 1.03; 95% CI 0.97 to 1.10). Additionally, there was no statistically significant difference in all-cause mortality between the tiotropium and placebo groups (Peto OR 0.98; 95% CI 0.86 to 1.11). However, subgroup analysis found a significant difference between the studies using a dry powder inhaler and those with a soft mist inhaler (test for subgroup differences: P = 0.01). With the dry powder inhaler there were fewer deaths in the tiotropium group (Peto OR 0.92; 95% CI 0.80 to 1.05) than in the placebo group (yearly rate 2.8%), but with the soft mist inhaler there were significantly more deaths in the tiotropium group (Peto OR 1.47; 95% CI 1.04 to 2.08) than in the placebo group (yearly rate 1.8%). It is noted that the rates of patients discontinuing study treatment were uneven, with significantly fewer participants withdrawing from tiotropium treatment than from placebo treatment (OR 0.66; 95% CI 0.59 to 0.73). Participants on tiotropium had improved lung function at the end of the study compared with those on placebo (trough forced expiratory volume in one second ($FEV_{1)}$ MD 118.92 mL; 95% CI 113.07 to 124.77).

**Authors' conclusions**

This review shows that tiotropium treatment was associated with a significant improvement in patients' quality of life and it reduced the risk of exacerbations, with a number needed to treat to benefit (NNTB) of 16 to prevent one exacerbation. Tiotropium also reduced exacerbations leading to hospitalisation but no significant difference was found for hospitalisation of any cause or mortality. Thus, tiotropium appears to be a reasonable choice for the management of patients with stable COPD, as proposed in guidelines. The trials included in this review showed a difference in the risk of mortality when compared with placebo depending on the type of tiotropium delivery device used. However, these results have not been confirmed in a recent trial when 2.5 mcg or 5 mcg of tiotropium via Respimat was used in a direct comparison to the 18 mcg Handihaler.

## PLAIN LANGUAGE SUMMARY

**Tiotropium for managing COPD**

Chronic obstructive pulmonary disease (COPD) is a lung disease which includes the conditions, chronic bronchitis and emphysema. It is caused by smoking or inhaled dust, which leads to blockage or narrowing of the airways. The symptoms include breathlessness and a chronic cough. Tiotropium is an inhaled medication that helps widen the airways (bronchodilator) for up to 24 hours, and is used to manage persistent symptoms of COPD.

We found 22 studies including 23,309 participants, comparing the long-term effectiveness and side effects of tiotropium and placebo. Compared with placebo, tiotropium treatment led to an improvement in quality of life, fewer people had an exacerbation (worsening of COPD symptoms), or exacerbations leading to hospital admissions. The number of people that needed to be treated for a year, for one person to avoid one additional exacerbation was 16 (95% confidence interval (CI) 10 to 36). We found no statistically significant difference between the tiotropium and placebo groups in terms of the number of hospital admissions for any cause, serious adverse events or deaths during the studies. However, when we divided the data depending on whether a dry powder inhaler or a soft mist inhaler was used in the studies, these two subgroups were significantly different. With the dry powder inhaler there were fewer deaths in the tiotropium group than in the placebo group, whereas with the soft mist inhaler there were significantly more deaths in the tiotropium group than in the placebo group. Also, there was a larger number of participants that stopped study medication early in the placebo group than in the tiotropium group.

This review shows that treatment with tiotropium improves patients' quality of life, and reduces the risk of exacerbations, including exacerbations leading to hospitalisation. But tiotropium does not reduce hospitalisations for all causes or the number of deaths. Based on the evidence in this review, tiotropium appears to be a reasonable treatment choice for patients with stable COPD.