Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials

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CRD summary
The authors concluded that this review provided a comparative safety spectrum for each category of inhaled medications. Tiotropium Soft Mist Inhaler had a higher risk of mortality and should be used with caution. With a small caveat regarding potential error and bias during the review, the authors’ cautious conclusions and recommendations seem warranted and reliable.

Authors' objectives
To compare the risks of overall and cardiovascular death for inhaled medications in patients with chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, CINAHL, ClinicalTrials.gov and The Cochrane Library were searched from inception to July 2011 for papers in English. Manufacturers' clinical trials registers were searched for unpublished trials. References of eligible trials and relevant systematic reviews were handsearched to locate further trials.

Study selection
Eligible studies were double-blind randomised active or placebo-controlled trials that evaluated the effects of tiotropium Soft Mist Inhaler, tiotropium HandiHaler, long-acting beta agonists (LABA), inhaled corticosteroids (ICS) or a combination of LABA and ICS in patients with COPD of any severity. The primary outcome of interest was all-cause death and the secondary outcome was death from cardiovascular causes. Included trials had last six months or more. Trials that included patients with asthma were excluded. Also excluded were trials with arms that received other treatments and trials published only in protocols or abstracts.

Mean ages of patients in treatment arms of the included trials ranged from 52.4 to 68.1 years. The proportion of male patients ranged from 3% to 99%. Where reported, the proportion of current smokers ranged from 18.9% to 100%. Mean baseline levels of forced expiratory volume (in one second) ranged from 32.6% to 86.9% of the predicted value. Some trials reported concomitant use of LABA (range 3% to 60.1%) or ICS (range 14% to 86.2%) among the trial groups. Study duration ranged from 24 weeks to four years.

It appeared that two reviewers independently selected studies for inclusion.

Assessment of study quality
Cochrane criteria were used to assess risk of bias with randomisation, allocation concealment, blinding of patients and personnel, objective adjudication of death, reporting of outcomes, withdrawal rates and loss to follow-up. Methods for monitoring adverse events were recorded.

It appeared that two reviewers independently assessed the quality of the studies.

Data extraction
Data on the outcomes (rates of all-cause and cardiovascular death) per study group were extracted from individual studies to calculate odds ratios and 95% confidence intervals. Any missing information on outcomes were obtained by contact with authors or a search of the US Food and Drug Administration website.

Three reviewers independently extracted data; any discrepancies were resolved by discussion and consensus.

Methods of synthesis
Direct comparisons were made by using the Peto method (for rare events) to pool odds ratios and 95% confidence
A fixed-effect Mantel-Haenszel meta-analysis with different continuity correction factors was performed as a sensitivity analysis. Statistical heterogeneity between studies was assessed using the $I^2$ statistic ($\geq50\%$ or more indicated substantial heterogeneity). Publication bias was assessed by funnel plot, Begg's test and Egger's test. A mixed treatment comparison meta-analysis was conducted using Bayesian Markov Monte Carlo methods and both random-effects and fixed-effect models to calculate pooled odds ratios and 95% credible intervals (CrI). The probability of overall and cardiovascular death per treatment and the probability of a treatment being ranked as the riskiest intervention were estimated.

Subgroup analyses were performed according to study duration and severity of COPD. A stratification analysis was performed to explore a possible dose-response relation of tiotropium Soft Mist Inhaler with other treatments. Meta-regression was performed to adjust for related demographic characteristics. Sensitivity analyses were conducted by removal of trials with the ICS withdrawal design and restriction to trials with objective adjudication of cause of death.

Results of the review

Forty-two randomised controlled trials (52,516 patients) were included in the review. All of the included trials reported blinding of patients and personnel. Randomisation methods and allocation concealment were both assessed as being adequately reported in 24 trials. Withdrawal rates (range from 17% in the tiotropium Soft Mist Inhaler group to 33% in ICS and placebo groups) were reported in 41 trials. Twenty-eight trials adequately reported loss to follow-up. Six trials described objective adjudication of cause of death.

Direct comparison meta-analysis: Compared with placebo, tiotropium Soft Mist Inhaler demonstrated a significantly increased risk of all-cause death (OR 1.49, 95% CI 1.05 to 2.11; three trials; $I^2=15.3\%$). Risk of all-cause death was significantly increased for tiotropium HandiHaler over LABA-ICS (OR 1.81, 95% CI 1.07 to 3.05; one trial).

Comparisons with placebo revealed a significantly increased risk of death from cardiovascular causes with tiotropium Soft Mist Inhaler (OR 1.96, 95% CI 1.07 to 3.60; two trials; $I^2=0\%$). Sensitivity analysis using the Mantel-Haenszel method did not differ substantially from the initial analysis (Peto method). No evidence of publication bias was found.

Mixed treatment comparison (fixed-effect) meta-analysis: Tiotropium Soft Mist Inhaler was associated with a universally increased risk of all-cause death compared with placebo (OR 1.51, 95% CrI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65, 95% CrI 1.13 to 2.43), LABA (OR 1.63, 95% CrI 1.10 to 2.44) and LABA-ICS (OR 1.90, 95% CrI 1.28 to 2.86).

Risk of death from cardiovascular causes was significantly increased for tiotropium Soft Mist Inhaler compared with placebo (OR 2.07, 95% CrI 1.09 to 4.16), tiotropium HandiHaler (OR 2.38, 95% CrI 1.20 to 4.99), LABA (OR 3.04, 95% CrI 1.48 to 6.55), LABA-ICS (OR 2.79, 95% CrI 1.37 to 6.02) and ICS (OR 2.39, 95% CrI 1.18 to 5.12). No moderate or substantial between-study heterogeneity was shown.

In the random-effects model, tiotropium Soft Mist Inhaler was consistently shown to have an increased risk of all-cause death compared with any comparator and demonstrated an increased risk of death from cardiovascular causes in comparison with LABA-ICS.

Further results were reported fully in the paper.

Authors' conclusions

This review provided a comparative safety spectrum for each category of inhaled medications. Tiotropium Soft Mist Inhaler had a higher risk of mortality and should be used with caution.

CRD commentary

The review question and inclusion criteria were clearly defined. Relevant databases were searched and an attempt was made to locate unpublished trials. The language restriction during the search meant that relevant trials in languages other than English may have been missed. No evidence of publication bias was found in the funnel plot and from statistical tests. Efforts were made to minimise reviewer error and bias during data extraction; it was unclear whether this also applied to study selection and quality assessment. Suitable quality assessment criteria were used and were reported fully in an appendix.
Study details were presented. Methods of synthesis seemed appropriate. The authors acknowledged that the validity of their findings may have been limited by factors related to their analyses (explained fully in paper) and generalisability limited by trials' frequent exclusion of patients with significant diseases and specific cardiovascular comorbidities.

With a small caveat regarding potential error and bias during study selection and quality assessment, the authors' cautious conclusions and recommendations seem warranted and reliable.

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

**Practice:** The authors stated that health professionals should use tiotropium Soft Mist Inhaler with caution and never exceed the recommended daily dose. Alternative treatments might be considered with high-risk populations such as those diagnosed with cardiac dysrhythmias or severe COPD.

**Research:** The authors stated a need for further studies to identify optimal therapeutic regimes and combinations for COPD patients, investigate standalone or add-on effects of combined LABA and ICS use and compare different formulations and doses of tiotropium.

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