Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review

Rodrigo GJ, Plaza V, Castro-Rodriguez JA

CRD summary
This review found that tiotropium plus a long-acting beta 2 agonist, with or without inhaled corticosteroids, appeared to be more effective than tiotropium alone for moderate-to-severe chronic obstructive pulmonary disease, but the data were scarce and follow-ups too short for firm conclusions. Overall, these conclusions appear to be suitably conservative.

Authors’ objectives
To assess the efficacy of three options versus tiotropium monotherapy for maintenance treatment of moderate-to-severe chronic obstructive pulmonary disease (COPD). The three options were a long-acting beta 2-agonist with the addition of tiotropium, inhaled corticosteroids, or both.

Searching
Searches of MEDLINE and EMBASE (January 1980 to May 2011) and the Cochrane Central Register of Controlled Trials (CENTRAL; first quarter 2011) were performed. Search terms were listed in the review. A search of relevant files from the drug manufacturers’ databases was performed. There were no language restrictions.

Study selection
Parallel or crossover randomised controlled trials (RCTs) were eligible for inclusion if they compared any of the three combination therapies with tiotropium monotherapy in adults aged over 40 years with stable COPD, defined by the American Thoracic Society/European Respiratory Society or Global Initiative for Chronic Obstructive Lung Disease criteria. Trials published solely as an abstract were excluded. Trials had to be of at least two weeks’ duration. The primary outcomes were: the forced expiratory volume in the first second (FEV1) before and after bronchodilator; the use of rescue medications; health-related quality of life, measured by the St. George Respiratory Questionnaire; dyspnoea; and COPD exacerbations. Secondary outcomes were: all-cause mortality, withdrawals during treatment, and severe adverse effects.

The included trials were crossover and parallel-group trials in single or multiple centres. The percentage of males ranged from 32 to 99 (mean 72), and the mean age ranged from 59 to 73 years (mean 64). Where stated, none to 82% were smokers, and in about half of the trials, patients used inhaled corticosteroids. The baseline percentage predicted FEV1 ranged from 30 to 80 (mean 41). Tiotropium was given at a dose of 18 micrograms once per day in all trials; the doses of other drugs were reported. Trials lasted from four to 104 weeks and five trials lasted for 24 weeks or longer.

Trial selection was performed independently by three reviewers; disagreements were resolved by group consensus.

Assessment of study quality
Trial quality was assessed using the Cochrane Risk of Bias tool to grade them as high, low, or unclear risk of bias on the following four items: allocation sequence generation; concealment of allocation; blinding of participants and investigators; and handling of missing data. The proportion of patients who completed each trial was reported.

Quality was assessed independently by three reviewers; disagreements were resolved by group consensus.

Data extraction
The data were extracted to calculate odds ratios for binary outcomes and mean differences for continuous outcomes, with associated 95% confidence intervals.

These data were extracted independently by three reviewers; disagreements were resolved by group consensus.

Methods of synthesis
The data were pooled by meta-analysis using random-effects models. If estimates were significantly different between
groups, the number needed to treat for benefit or for harm was calculated. Pre-specified subgroup analyses were performed, grouping trials by type of beta 2 agonist (formoterol, salmeterol, or indacaterol) and length of treatment (less than 24 weeks, or 24 weeks or more).

Statistical heterogeneity was assessed using $I^2$, and classified as follows: under 40% might be unimportant; 40% to 60% might be moderate; and 60% to 100% might be substantial. For outcomes that showed statistically significant differences, but moderate to substantial heterogeneity, 95% prediction intervals were calculated to show the distribution of true effect sizes.

Publication bias was assessed by examination of funnel plots.

Results of the review
Twenty trials, with 6,803 participants, were included. Allocation concealment was adequate in eight trials and all but two were adequately blinded. Between 61% and 98% of participants completed each trial; these data were not collected in 12 trials. Ten trials were sponsored by the pharmaceutical industry.

Long-acting beta 2 agonist plus tiotropium: Ten trials were found. Tiotropium plus a long-acting beta 2 agonist was associated with improvements in all FEV1 outcomes, compared with tiotropium monotherapy; details were reported. Funnel plots did not suggest publication bias for the pulmonary function outcomes. Combined treatment was also associated with less rescue medication (seven trials), improvement in health-related quality of life (five trials), and a lower transitional dyspnoea index (five trials). There was no difference between groups in the other outcomes. There was significant heterogeneity in the mean change in pre-bronchodilator trough FEV1 from baseline, the use of rescue medication, and dyspnoea. The 95% prediction intervals suggested that these effects might not be statistically significant in all settings.

Long-acting beta 2 agonist plus inhaled corticosteroids: Seven trials were found. Compared with tiotropium monotherapy, combined treatment was associated with a higher mean final pre-bronchodilator FEV1 (WMD 60mL, 95% CI 10 to 120; two trials); a higher mean change in pre-bronchodilator trough FEV1 from baseline (WMD 60mL, 95% CI 10 to 100; five trials); less use of rescue medication (0.4 fewer puffs per day, 95% CI -0.76 to -0.03; five trials); and improvement in health-related quality of life (WMD -2.07, 95% CI -2.49 to -1.64; two trials). There was a higher risk of serious adverse events (OR 1.33, 95% CI 1.04 to 1.69; four trials) and a higher risk of pneumonia (OR 2.22, 95% CI 1.35 to 3.63; two trials). None of the other outcomes differed between the two groups.

Long-acting beta 2 agonist plus tiotropium and inhaled corticosteroids: Six trials were found. Compared with tiotropium monotherapy, combined treatment was associated with better FEV outcomes; details were reported. The authors reported significant improvement in health-related quality of life. There appears to be an error in the paper, since some reported confidence intervals are not compatible with reported probabilities.

Authors' conclusions
Tiotropium plus a long-acting beta 2 agonist, with or without inhaled corticosteroids, appeared to be more effective than tiotropium monotherapy for moderate-to-severe COPD, but data were scarce and follow-ups too short for firm conclusions.

CRD commentary
This review addressed a clear research question. The search covered a range of relevant sources, without language restrictions. Participant, intervention, design and outcome criteria were clearly stated, and the authors attempted to minimise error and bias at all stages of the review process. They attempted to locate unpublished trials (and included five of them), but noted that a formal test of publication bias could not be performed for many outcomes because of the small number of trials.

The quality of included trials was assessed using appropriate criteria and they were of variable quality. The meta-analysis included crossover and parallel trials, but the authors did not explain how these different types of trial were synthesised in one analysis. The authors used prediction intervals to better understand the true effects where there was statistical heterogeneity, but they did not explore the reasons for this heterogeneity.

There were a large number of primary outcomes, which made the results and implications hard to interpret. Overall, the
authors’ conclusions reflect the evidence presented and appear to be suitably cautious.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further large, long-term RCTs were required to compare combined pharmacological approaches with tiotropium alone. The long-term efficacy and safety of the different combinations, and their effects on the natural history of COPD when used early in disease progression, should be investigated.

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