The effect of adding inhaled corticosteroids to tiotropium and long-acting beta$_2$-agonists for chronic obstructive pulmonary disease (Review)

Karner C, Cates CJ

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[Intervention Review]

The effect of adding inhaled corticosteroids to tiotropium and long-acting beta$_2$-agonists for chronic obstructive pulmonary disease

Charlotta Karner[1], Christopher J Cates[1]

[1]Population Health Sciences and Education, St George's, University of London, London, UK

Contact address: Charlotta Karner, Population Health Sciences and Education, St George's, University of London, London, UK. ckarner@sgul.ac.uk.

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ABSTRACT

Background

Long-acting bronchodilators comprising long-acting beta$_2$-agonists and the anticholinergic agent tiotropium are commonly used, either on their own or in combination, for managing persistent symptoms of chronic obstructive pulmonary disease. Patients with severe chronic obstructive pulmonary disease who are symptomatic and who suffer repeated exacerbations are recommended to add inhaled corticosteroids to their bronchodilator treatment. However, the benefits and risks of adding inhaled corticosteroid to tiotropium and long-acting beta$_2$-agonists for the treatment of chronic obstructive pulmonary disease are unclear.

Objectives

To assess the relative effects of adding inhaled corticosteroids to tiotropium and long-acting beta$_2$-agonists treatment in patients with chronic obstructive pulmonary disease.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials (February 2011) and reference lists of articles.

Selection criteria

We included parallel group, randomised controlled trials of three months or longer comparing inhaled corticosteroid and long-acting beta$_2$-agonist combination therapy in addition to inhaled tiotropium against tiotropium and long-acting beta$_2$-agonist treatment for patients with chronic obstructive pulmonary disease (COPD).

Data collection and analysis

Two review authors independently assessed trials for inclusion and then extracted data on trial quality and the outcome results. We contacted study authors for additional information. We collected information on adverse effects from the trials.

Main results

One trial (293 patients) was identified comparing tiotropium in addition to inhaled corticosteroid and long-acting beta$_2$-agonist combination therapy to tiotropium plus long-acting beta$_2$-agonist. The study was of good methodological quality, however it suffered from high and uneven withdrawal rates between the treatment arms. There is currently insufficient evidence to know how much difference the addition of inhaled corticosteroids makes to people who are taking tiotropium and a long-acting beta$_2$-agonist for COPD.

Authors' conclusions

The relative efficacy and safety of adding inhaled corticosteroid to tiotropium and a long-acting beta$_2$-agonist for chronic obstructive pulmonary disease patients remains uncertain and additional trials are required to answer this question.

PLAIN LANGUAGE SUMMARY

The effect of adding inhaled corticosteroids to tiotropium and long-acting beta$_2$-agonists for managing chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a lung disease which includes the conditions chronic bronchitis and emphysema. COPD is characterised by blockage or narrowing of the airways. The symptoms include breathlessness and a chronic cough. COPD is an irreversible disease that is usually brought on by airway irritants, such as smoking or inhaled dust.

Long-acting beta$_2$-agonists and tiotropium are two types of inhaled medications that help widen the airways (bronchodilators) for up to 12 to 24 hours. These bronchodilators are commonly used to manage persistent symptoms of COPD. They can be used in combination or on their own. Patients with severe COPD who suffer ongoing worsening of symptoms are recommended to add anti-inflammatory inhaled corticosteroids to their bronchodilator treatment. However, the benefits and risks of adding inhaled corticosteroid to tiotropium and long-acting beta$_2$-agonists for the treatment of COPD are unclear.

This review found one study, involving 293 patients, comparing the long-term efficacy and side effects of combining inhaled corticosteroid with tiotropium and a long-acting beta$_2$-agonist. In this study there were not enough patients for us to be able to draw any firm conclusions as to whether combining inhaled corticosteroid with tiotropium and the long-acting beta$_2$-agonist is better or worse than using only tiotropium and the long-acting beta$_2$-agonist. More long-term studies need to be done in order to better understand the effect of treatment with inhaled corticosteroid, tiotropium and a long-acting beta$_2$-agonist.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterised by chronic and progressive breathlessness, cough, sputum production, and airflow obstruction, which leads to restricted activity and poor quality of life (GOLD). COPD comprises a combination of bronchitis and emphysema and involves chronic inflammation and structural changes in the lung. Cigarette smoking is the most important risk factor, however air pollution and occupational dust and chemicals are also recognised risk factors. The World Health Organization (WHO) has estimated that COPD is the fourth or fifth most common single cause of death worldwide and the treatment and management costs present a significant burden to public health. Furthermore, because of the slow onset and the under-recognition of the disease, it is heavily under-diagnosed (GOLD). COPD is a progressive disease leading to decreased lung function over time, even with the best available care. There is currently no cure for COPD though it is both a preventable and treatable disease. As yet, apart from smoking cessation and non-pharmacological treatments such as long-term oxygen therapy in hypoxic patients, no intervention has been shown to reduce mortality (GOLD). Management of the disease is multifaceted and includes reducing risk factors (van der Meer 2001), pharmacological treatments (GOLD; NICE 2010), education (Effing 2007) and pulmonary rehabilitation (Lacasse 2006). Pharmacological therapy is aimed at relieving symptoms, improving exercise tolerance and quality of life, improving lung function, or preventing and treating exacerbations. COPD exac-

erbations impair patients' quality of life (GOLD). Furthermore, a large part of the economic burden of COPD is attributed to the cost of managing exacerbations, particularly those resulting in use of acute care services or hospitalisations (Hutchinson 2010). Appropriate pharmacological management of the disease is therefore important to reduce and prevent exacerbations.

Description of interventions

COPD pharmacological management tends to begin with one treatment and additional therapies are introduced, as necessary, to control symptoms (GOLD). The first step is often a short-acting bronchodilator for control of breathlessness, when needed: either a short-acting beta$_2$-agonist (SABA) or the short-acting anticholinergic ipratropium. For persistent or worsening breathlessness associated with lung function decline long-acting bronchodilators may be introduced (GOLD). Long-acting bronchodilators include long-acting beta$_2$-agonists (LABA), such as salmeterol or formoterol, and the long-acting anticholinergic agent tiotropium. Regular treatment with long-acting bronchodilators may be more efficient and convenient than treatment with regular short-acting bronchodilators (Beeh 2010). However, the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines do not specify a preference between the two drug classes. For symptomatic patients with severe or very severe COPD (FEV_1 < 50% predicted) and with repeated exacerbations GOLD recommends the addition of inhaled corticosteroids (ICS) to bronchodilator treatment. The potential risks or benefits of treatment with a LABA and ICS combination inhaler compared to tiotropium are uncertain (Welsh 2010), as are the risks or benefits of treatment with a combination inhaler in addition to tiotropium, which will be explored in this review.

How the intervention might work

Tiotropium

Tiotropium is an anticholinergic agent, blocking the action of the neurotransmitter acetylcholine. It has an antagonistic effect on muscarinic acetylcholine receptors. Tiotropium has similar affinity for the five different subtypes of muscarinic receptors (M1 to M5), however airway smooth muscle expresses only the M2 and M3 subtypes (Proskocil 2005). Activation of the M3 receptor stimulates a number of intracellular signalling cascades leading to changes in intracellular Ca^{2+} homeostasis and contraction of smooth muscle. Tiotropium dissociates slowly from M3 receptors giving a bronchodilator effect lasting over 24 hours, but it dissociates rapidly from M2 receptors, which appear to be feedback inhibitory receptors (Barr 2005).

Tiotropium has gained widespread acceptance for its effects on symptoms and exacerbations as a once daily maintenance therapy in stable COPD (Barr 2005; GOLD). In an earlier Cochrane review (Barr 2005), tiotropium was shown to reduce the primary endpoint of COPD exacerbations compared to placebo (OR 0.75; 95% CI 0.66 to 0.85). Within the same review, tiotropium was also associated with a significant benefit over placebo measuring breathlessness, quality of life and a reduction in exacerbations requiring hospitalisation. Similar effects on symptoms and exacerbations were confirmed in a more recent, large randomised control trial of almost 6000 patients followed for over four years (Tashkin 2008). There was, however, no significant effect of tiotropium on lung function decline in this longer study. Anticholinergic side effects that may occur with tiotropium include dry mouth, constipation and tachycardia (Tashkin 2008).

Inhaled corticosteroids (ICS) and long-acting beta$_2$-agonist (LABA)

Inhaled beta$_2$-agonists activate beta$_2$-receptors in the smooth muscle of the airway leading to a cascade of reactions that results in bronchodilation. Beta$_2$-agonists may also act through other mechanisms, such as respiratory muscle function or mucociliary clearance, because patients have shown improvement in symptoms whilst showing no improvement in lung function tests. Beta$_2$-agonists are particularly useful bronchodilators because they reverse bronchoconstriction regardless of the initial cause. The commonly used long-acting beta$_2$-agonists, salmeterol and formoterol, both have a higher selectivity for beta$_2$-receptors than beta$_1$-receptors. Beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the heart, although 10% to 50% of the total beta-receptors in the heart are comprised of beta$_2$-receptors (Wallukat 2002). The presence of beta$_2$-receptors in the heart raises the possibility that even highly selective beta$_2$-agonists may have cardiac effects. The mechanism for activating beta$_2$-receptors differs between formoterol and salmeterol. Formoterol is taken up into a membrane depot from where it gradually leaks out to interact with the receptor, whilst salmeterol binds near the receptor allowing it to remain at the receptor site continually binding and releasing (Johnson 1998). In both cases stimulation of the beta$_2$-receptors leads to changes in intracellular Ca^{2+} homeostasis and bronchodilation (Tanaka 2005). The duration of action for long-acting beta$_2$-agonists is approximately 12 hours, and LABAs are usually taken twice daily.

As with tiotropium, LABAs are used as 'symptom controllers' in stable COPD. A prior Cochrane review found that LABAs improve lung function compared to placebo (Appleton 2006). A more recent, large (3045 patients) long-term (three year) randomised controlled trial compared salmeterol to placebo (TORCH) (Calverley 2007). Salmeterol use was associated with an increase in lung function and a significant reduction in moderate or severe exacerbations compared with placebo (OR 0.85, P < 0.001). A systematic review which included the TORCH study

and another 13 trials, with a total of 6453 participants, showed that treatment with a LABA reduced the rate of exacerbations and improved lung function and quality of life compared to placebo but had no effect on mortality (Rodrigo 2008). Possible side effects of LABAs include cardiac effects such as arrhythmia and palpitations, muscle tremors, head ache and dry mouth (Berger 2008).
Inhaled corticosteroids are anti-inflammatory drugs. They reduce the rate of exacerbations and the rate of decline in quality of life compared to placebo without any effect on overall mortality or the long-term decline in FEV_1 (Agarwal 2010; GOLD; Yang 2007). Inhaled corticosteroids are licensed as combination inhalers with long-acting $beta_2$-agonists. The most common combinations of inhaled corticosteroid and long-acting $beta_2$-agonist in combination inhalers are fluticasone and salmeterol and budesonide and formoterol. Combination inhalers reduce exacerbation rates and all-cause mortality, and improve lung function and quality of life compared to placebo (Nannini 2007). These effects are thought to be greater for combination inhalers than with the component preparations (GOLD). However, inhaled corticosteroids, alone or in combination with $beta_2$-agonists, may increase the risk of pneumonia (GOLD; Singh 2010).

Why it is important to do this review

Patients with severe COPD who are symptomatic and have repeated exacerbations are recommended to add inhaled corticosteroids (ICS) to their bronchodilator treatment (LABA, anticholinergic, or both), most commonly using LABA and ICS combination inhalers. It is unclear what potential clinical advantages arise by combining tiotropium with LABA and ICS compared to tiotropium plus LABA only for these patients. It has been suggested that adding combination inhaler therapy to tiotropium treatment may be beneficial for exacerbations and hospitalisations, which are important sources of healthcare resource utilisation and the cost in COPD (Najafzadeh 2008). This review is necessary to specify and quantify the potential benefits from the combination treatment with LABA, ICS and tiotropium compared to LABA and tiotropium.
This review will form part of a suite of reviews on the various combinations of tiotropium, long-acting $beta_2$-agonists and inhaled corticosteroids for the treatment of COPD. These reviews will ultimately be summarised in an overview. The first of these reviews compared a combination of inhaled corticosteroids and long-acting $beta_2$-agonist with tiotropium (Welsh 2010) and further reviews are in preparation comparing alternate permutations of these three drugs.

OBJECTIVES

To compare the relative effects on measures of quality of life, exacerbations, lung function and serious adverse events in patients with chronic obstructive pulmonary disease randomised to the following therapies:

- inhaled tiotropium, long-acting $beta_2$-agonist and corticosteroid versus inhaled tiotropium and long-acting $beta_2$-agonist.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials with a parallel group design of at least 12 weeks duration. We did not exclude studies on the basis of blinding.

Types of participants

We included populations with a diagnosis of chronic obstructive pulmonary disease. We only included studies where an external set of criteria had been used to screen participants for this condition (for example Global Initiative for Obstructive Lung Disease (GOLD), American Thoracic Society (ATS), British Thoracic Society (BTS), The Thoracic Society of Australia and New Zealand (TSANZ)).

Types of interventions

Inhaled corticosteroid and long-acting $beta_2$-agonist (in either a single combination inhaler or two separate inhalers) and tiotropium bromide compared to inhaled long-acting $beta_2$-agonists and tiotropium administered by any inhalation device.

Types of outcome measures

Primary outcomes

1. Quality of life (measured with a validated scale for COPD, e.g. St George's Respiratory Questionnaire, Chronic Respiratory Disease Questionnaire)
2. Exacerbations, requiring short burst oral corticosteroids or antibiotic, or both
3. Pneumonia
4. Mortality, all-cause

Secondary outcomes

1. Hospital admissions, all causes and due to exacerbations
2. Disease specific mortality, if independently adjudicated
3. Forced expiratory volume in one second (FEV_1)
4. Serious adverse events, all-cause, non-fatal
5. Withdrawals

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO; and handsearching of respiratory journals and meeting abstracts (please see the Airways Group search methods for further details). The search was not limited by language. All records in the Specialised Register coded as 'COPD' were searched using the following terms:
(tiotropium or spiriva)
AND
(((budesonide or fluticasone or beclomethasone or mometasone or ciclesonide or steroid* or corticosteroid*) and (*formoterol or salmeterol or indacaterol or (beta* and agonist*))) or (symbicort or viani or seretide or advair or foster or fostair or inuvair or fostex or kantos or combination*))
We also conducted a search of clinicaltrials.gov. The search was carried out in February 2011.

Searching other resources

We reviewed the reference lists of the primary study and review articles for references to other trials. We contacted authors of identified trials and manufacturers to ask them to identify other published or unpublished studies.

Data collection and analysis

Selection of studies

Both of us screened the titles and abstracts of citations retrieved through literature searches and obtained those deemed to be potentially relevant. We assigned each reference to a study identifier and assessed them against the inclusion criteria of this protocol.

Data extraction and management

We extracted information from the included study for the following characteristics:

1. design (design, total duration study and run in, number of study centres and location, withdrawals, date of study);
2. participants (N, mean age, age range, gender, COPD severity, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, exclusion criteria);
3. interventions (run-in, intervention treatment and inhaler type, control treatment and inhaler type);
4. outcomes (primary and secondary outcomes specified and collected, time points reported).

Both of us extracted data from the study into a data collection form. We discussed and resolved any discrepancies in the data, or consulted a third party where necessary. We transferred data from the data collection forms into Review Manager 5.

Assessment of risk of bias in included studies

We assessed the risk of bias according to recommendations outlined in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) for the following items:

1. allocation sequence generation;
2. concealment of allocation;
3. blinding of participants and investigators;
4. incomplete outcome data;
5. selective outcome reporting.

We graded each potential source of bias as low, high or unclear risk of bias. We also planned to note other sources of bias.

Measures of treatment effect

Dichotomous data

We analysed dichotomous data variables (such as mortality and withdrawals) using Mantel-Haenszel odds ratios using a fixed-effect model with 95% confidence intervals (CI). If events had been rare we would have employed the Peto odds ratio since this does not require a continuity correction for zero cells. If count data had not been available as the number of participants experiencing an event, we would have analysed it as continuous, time-to-event or rate ratios depending on how it had been reported. This included the outcomes: hospital admissions, exacerbations, and serious adverse events. Reported rate ratios would have been transformed into log rate ratios and analysed using a fixed-effect model and the generic inverse variance (GIV) in Review Manager 5.

Continuous data

We analysed continuous outcome data (such as FEV_1 and quality of life) as fixed-effect model mean differences (MD) with 95% confidence intervals. If more than one study had been included in the review, we would have analysed continuous outcome data as fixed-effect model mean differences if the same scale had been used, and standardised mean differences if different scales had been employed in different studies. If treatment effects had been reported as a mean difference with a CI or an exact P value, we would have calculated the standard error and entered it with the mean difference and combined the results using a fixed-effect GIV model in Review Manager 5. If data had not been available for the same time point in all studies, the closest time points would have been used. The second alternative would have been to use end of study as the time of analysis for all studies.

We planned to use intention-to-treat (ITT) analysis on outcomes, from all randomised participants where possible, for primary analyses.

We planned to calculate the numbers needed to treat from the pooled odds ratio and its confidence interval and to apply it to appropriate levels of baseline risk.

Unit of analysis issues

We analysed dichotomous data using participants as the unit of analysis (rather than events) to avoid counting the same participant more than once. For continuous data the mean difference based on change from baseline was preferred over mean difference based on absolute values.

Dealing with missing data

We contacted the study investigators in order to verify key study characteristics and to obtain missing numerical outcome data where possible. We also planned to consider the impact of the unknown status of participants who withdrew from the trials as part of a sensitivity analysis.

Assessment of heterogeneity

We planned to assess the amount of statistical variation between study results with the I^2 statistic.

Assessment of reporting biases

We minimised reporting bias from non-publication of studies or selective outcome reporting by using a broad search strategy, contacting study authors directly and checking references of included studies. If we found sufficient numbers of trials, we planned to visually inspect funnel plots.

Data synthesis

We planned to present the findings of our primary outcomes in a summary of findings table using GradePro software and the recommendations outlined in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), if there had been more than one eligible study.

Subgroup analysis and investigation of heterogeneity

We planned to subgroup studies according to:

1. types of long-acting beta-agonist and inhaled corticosteroid;
2. severity of disease at baseline;
3. tiotropium formulation.

Sensitivity analysis

We planned to assess the sensitivity of our primary outcomes to degree of bias by comparing the overall results with those exclusively from trials assessed as being at low risk of bias.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

An initial search (July 2010) gave 101 references and additional searches gave a further 16 references (February 2011) and nine references (July 2011). Of the total 126 references we identified nine as potentially relevant, which we obtained in full text for further assessment. Five of these citations were eligible for inclusion and they all belonged to the study Aaron 2007 (see Characteristics of included studies).

Included studies

Aaron 2007 was a randomised, double-blind, placebo-controlled trial with a parallel group design. The duration of the study was one year and it was conducted in 27 different medical centres in Canada. There were 293 participants randomised to tiotropium + LABA and ICS (145) and tiotropium + LABA (148). The mean age of the participants was 68 years, the mean FEV_1 predicted was 39%, the gender distribution was 58% males and 42% women, and the disease severity of the participants spanned moderate to severe COPD according to the GOLD guideline definitions of COPD. The participants were either given 18 µg of tiotropium

(Handihaler) one inhalation daily plus 250 and 25 µg fluticasone and salmeterol (Diskus) two inhalations twice daily or 18 µg of tiotropium (Handihaler) plus 25 µg salmeterol (Diskus) two inhalations twice daily. Participants were instructed to use inhaled albuterol when necessary to relieve symptoms. Respiratory medications such as oxygen, antileukotrienes and methylxanthines, were continued in all patient groups. The primary outcome was the proportion of patients suffering one or more COPD exacerbations. The study was funded by the Canadian Institutes of Health Research and the Ontario Thoracic Society.

Excluded studies

Four studies failed to meet the eligibility criteria for the review (see Characteristics of excluded studies). All four lacked a tiotropium plus LABA treatment group. Three of them were also of cross-over design with a treatment period shorter than 12 weeks (Golabi 2006; Hara 2007; Mittmann 2010; Singh 2008).

Risk of bias in included studies

An assessment of the risk of bias is presented in the Characteristics of included studies table.

Allocation

Aaron 2007 reported adequate sequence generation and allocation concealment. Sequence generation was computer-generated and the different inhalers were identical.

Blinding

The blinding in Aaron 2007 was adequate. Both research staff and patients were blinded to the treatment assignment, and clinical data for suspected exacerbations were reviewed by a blinded committee.

Incomplete outcome data

Aaron 2007 suffered from high and uneven withdrawal rates in the different study groups (26% withdrew from the tiotropium + LABA and ICS group and 43% who were on tiotropium + LABA). For most patients, data were recorded throughout the one-year trial period regardless of whether patients discontinued treatment with the study medications. The rate of patients who stopped therapy and did not complete the trial, however, was still relatively large and unevenly distributed between the intervention groups (10% tiotropium + LABA and ICS, and 14% tiotropium + LABA). Mortality data were obtained for all participants with the exception of two participants (1.4%) on tiotropium + LABA and ICS and two (1.4%) on tiotropium + LABA who withdrew and declined further study.

Selective reporting

Aaron 2007 adequately reported outcome data for the primary and secondary outcomes that were pre-specified in the study record.

Effects of interventions

Data and analyses are summarised in Table 1.

Primary outcomes

Aaron 2007 (293 participants) studied changes in health-related quality of life using the St George's Respiratory Questionnaire (SGRQ). A decrease in SGRQ score indicates an improvement in quality of life and the threshold is four units for a clinically significant difference (SGRQ-C manual 2008). At the end of the study there was substantial uncertainty regarding the difference in effect of tiotropium + LABA and ICS and the tiotropium + LABA treatments on quality of life (MD -1.02; 95% CI -5.10 to 3.06).
Aaron 2007 defined COPD exacerbations as a sustained worsening of the patient's respiratory condition necessitating short-term use of either oral or intravenous steroids, oral or intravenous antibiotics, or both therapies. There was considerable uncertainty and no statistically significant difference in the number of patients who had one or more exacerbations between the tiotropium + LABA and ICS (87/145) and the tiotropium + LABA (96/148) groups (OR 0.81; 95% CI 0.51 to 1.30).
Aaron 2007 reported one case of pneumonia (leading to mechanical ventilation or death) and six deaths (all-cause) in each of the treatment groups. There was considerable uncertainty and no statistically significant differences between the treatment groups (pneumonia: OR 1.02; 95% CI 0.06 to 16.48, and mortality: OR 1.02; 95% CI 0.32 to 3.24).

Secondary outcomes

Data regarding hospitalisations due to exacerbations or any cause were kindly supplied by Aaron 2007 on request. There was no statistically significant difference in the number of patients admitted to hospital due to exacerbation or any cause between the treatment groups (all cause hospitalisation: tiotropium + LABA and ICS 32/145, tiotropium + LABA 35/148, OR 0.91 (95% CI 0.53 to 1.58), and due to exacerbation: tiotropium + LABA and ICS 20/145, tiotropium + LABA 30/148, OR 0.63 (95% CI 0.34 to 1.17)).
Tiotropium + LABA showed no significant difference in pre-bronchodilator FEV_1 compared to tiotropium + LABA and ICS (MD 0.07 L; 95% CI -0.03 to 0.17).
There was no statistically significant difference between tiotropium + LABA and ICS (3/145) and tiotropium + LABA (3/148) treatments in the number of patients suffering non-fatal serious adverse events (OR 1.02; 95% CI 0.20 to 5.14). More patients suffered adverse events on tiotropium + LABA and ICS (44/145)

than on tiotropium + LABA (32/148) (OR 1.58; 95% CI 0.93 to 2.68), although the difference was not statistically significant.

The number of withdrawals from Aaron 2007 for any reason was high and the withdrawal rate was significantly higher in the tiotropium + LABA group (43%) than in the tiotropium + LABA and ICS group (26%) (OR 0.45; 95% CI 0.27 to 0.74). Aaron 2007 reported the breakdown of the reasons for withdrawing from the study treatment, which included: adverse event, declined further study, lost to follow up, or lack of efficacy. Lack of efficacy was the sum of patients withdrawn from the study treatment because of treatment failure according to physician and patient perceptions of worsening of COPD. The difference between the number withdrawing due to adverse events (OR 1.38; 95% CI 0.47 to 4.09) was not statistically significant, whereas the difference between the number withdrawing due to lack of efficacy was significantly lower in the tiotropium + LABA and ICS group (25/145) than in the tiotropium + LABA group (54/148) (OR 0.36; 95% CI 0.21 to 0.63).

DISCUSSION

This systematic review set out to investigate the long-term (≥ three month) effect of tiotropium in combination with LABA and ICS compared to tiotropium + LABA for the treatment of COPD. One randomised, double-blind trial with 293 participants was identified. The Aaron 2007 study was of good methodological quality, however it suffered from high and uneven withdrawal rates between the treatment arms. The data from Aaron 2007 showed considerable uncertainty and no statistically significant difference between patients treated with tiotropium + LABA and ICS, and tiotropium + LABA for the outcomes: health-related quality of life, exacerbations, pneumonia, mortality, hospitalisations, FEV_1 and adverse events. The fact that only one, relatively small study was included in this review and that is suffered large and uneven withdrawals makes the results for outcomes with few events or small differences less reliable. However, the statistically significant difference in the number of patients who withdrew due to lack of efficacy may imply some beneficial effect of ICS and LABA + tiotropium compared to LABA + tiotropium treatment. Around 75% of participants in both treatment groups received ICS or ICS and LABA combination therapy before entering the trial (Aaron 2007). If the participants who were on ICS treatment at the time of randomisation represents ICS responders, this could lead to greater drop-outs in the placebo arm when these patients noticed a lack of benefit.

Several systematic reviews have tried to investigate the contribution of ICS to the benefits and risks of combination therapies in COPD. Systematic reviews comparing ICS treatment with placebo and LABA and ICS combination treatment to LABA alone have shown that ICS reduces the occurrence of exacerbations (Agarwal 2010; Nannini 2007a; Rodrigo 2009) and has positive effects on quality of life and lung function (Nannini 2007a; Rodrigo 2009; Yang 2007). ICS treatment on its own or in combination with LABA has not been shown to have any significant effect on mortality (Nannini 2007a; Rodrigo 2009; Yang 2007). However, pneumonia occurs more frequently with ICS treatment and the elevated risk remained consistent irrespective of whether LABA and ICS combination inhalers were compared to LABA, ICS or to placebo (Nannini 2007a; Rodrigo 2009; Singh 2010). The potential effect of ICS on medical expenses for COPD patients has also been evaluated. Compared to placebo, ICS reduces costs and improves outcomes in patients aged over 50 years, although estimated cost saving per avoided exacerbation is uncertain (Akazawa 2008). The cost effectiveness of LABA and ICS combination therapy compared to LABA monotherapy seems to favour combination therapy based on a significant gain in quality-adjusted life years (Briggs 2010) and potentially an overall savings in total COPD-related exacerbation and therapeutic healthcare costs (Dalal 2010).

In summary, because of the limited evidence presented in this review, It is unclear if adding ICS to tiotropium + LABA will lead to similar clinical improvements, risks and cost effectiveness as when added to LABA monotherapy or placebo.

AUTHORS' CONCLUSIONS

Implications for practice

There was only a single study conducted with few patients and therefore there are insufficient data to draw any conclusions regarding the long-term effects and risks of tiotropium + LABA and ICS treatment compared to tiotropium + LABA. The relative efficacy and safety of adding ICS to tiotropium + LABA therefore remain uncertain.

Implications for research

Additional large, long-term randomised controlled trials are required to show any potential benefits and risks of taking LABA and ICS combination inhaler together with tiotropium rather than only tiotropium and LABA for COPD patients.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aaron 2007

Methods	**Design:** A randomised, double-blind, placebo-controlled, parallel group trial from October 2003 to January 2006. The trial included 27 Canadian medical centres; 20 centres were academic hospital-based pulmonary clinics, 5 were community-based pulmonary clinics, and 2 were community-based primary care clinics
Participants	**Population**: 293 adults with a clinical history of moderate or severe COPD as defined by ATS and GOLD guidelines **Baseline Characteristics**: Mean age 68 years. COPD severity moderate to severe with mean FEV_1 predicted of 39%. 58% men. **Inclusion Criteria**: At least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomisation; age older than 35 years; a history of 10 pack-years or more of cigarette smoking; documented chronic airflow obstruction, with an FEV_1/FVC ratio < 0.70 and a post-bronchodilator FEV_1 < 65% of the predicted value. **Exclusion Criteria**: History of physician-diagnosed asthma before 40 years of age; history of physician-diagnosed chronic congestive heart failure with known persistent severe left ventricular dysfunction; those receiving oral prednisone; those with a known hypersensitivity or intolerance to tiotropium, salmeterol, or fluticasone-salmeterol; history of severe glaucoma or severe urinary tract obstruction, previous lung transplantation or lung volume reduction surgery, or diffuse bilateral bronchiectasis; and those who were pregnant or were breastfeeding
Interventions	**1**. Tiotropium + salmeterol + fluticasone: tiotropium (Spiriva, Handihaler (Boehringer Ingelheim Pharma, Ingelheim, Germany)), 18 g once daily, plus fluticasone-salmeterol (Advair (GlaxoSmithKline)), 250/25 g/puff, 2 puffs twice daily **2**. Tiotropium + salmeterol: tiotropium, 18 g once daily, plus salmeterol (Serevent (GlaxoSmithKline, Research Triangle Park, North Carolina)), 25 g/puff, 2 puffs twice daily
Outcomes	**Primary**: Proportion of patients with one or more exacerbation of COPD **Secondary**: Mean number of COPD exacerbations per patient-year; the total number of exacerbations that resulted in urgent visits to a healthcare provider or emergency department; the number of hospitalisations for COPD; the total number of hospitalisations for all causes; changes in health-related quality of life, dyspnoea, lung function
Notes	**Co-medication**: All study patients were provided with inhaled albuterol and were instructed to use it when necessary to relieve symptoms. Any treatment with inhaled corticosteroids, long-acting $beta_2$-agonists, and anticholinergics that the patient may have been using before entry was discontinued on entry into the study. Therapy with other respiratory medications, such as oxygen, antileukotrienes, and methylxanthines, was continued in all patient groups

Risk of bias

Bias	Authors' judgement	Support for judgement

Aaron 2007 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomisation was done through central allocation of a randomisation schedule that was prepared from a computer-generated random listing of the 3 treatment allocations, blocked in variable blocks of 9 or 12 and stratified by site
Allocation concealment (selection bias)	Low risk	The metered-dose inhalers containing placebo, salmeterol, and fluticasone-salmeterol were identical in taste and appearance, and they were enclosed in identical tamper-proof blinding devices. The medication canisters within the blinding devices were stripped of any identifying labelling
Blinding (performance bias and detection bias) All outcomes	Low risk	Neither research staff nor patients were aware of the treatment assignment before or after randomisation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of people who stopped drug therapy was high, with large variations between the groups (37/145 (26%) tiotropium + LABA/ICS and 64/148 (43%) tiotropium + LABA). However, the number of people who did not complete the trial was lower, although there was still some variations between the groups (15 (10%) tiotropium + LABA/ICS and 20 (14%) tiotropium + LABA). The issue of incomplete data was however addressed by sensitivity analyses of the data for the primary outcome (exacerbations). In the primary analysis it was assumed that all patients who were lost to follow-up did not have an exacerbation (ITT analysis). In the sensitivity analyses it was assumed that patients who were lost to follow-up either all had an exacerbation or had exacerbations at the same rate as those who continued in the study. Both analyses gave a similar result to the primary ITT analysis
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Golabi 2006	Four weeks of treatment, only tiotropium alone and salmeterol/fluticasone treatment groups, cross-over design
Hara 2007	Eight weeks of treatment, only tiotropium alone and salmeterol/fluticasone treatment groups, cross-over design
Mittmann 2010	No tiotropium plus LABA treatment group
Singh 2008	Two weeks of treatment, no tiotropium plus LABA treatment group, and of cross-over design

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Data analysis summary

Outcome	Effect estimate
Quality of life (SGRQ)	MD -1.02; 95% CI -5.10 to 3.06
Number of patients with ≥1 exacerbations	OR 0.81; 95% CI 0.51 to 1.30
Number of patients suffering from pneumonia	OR 1.02; 95% CI 0.06 to 16.48
Mortality	OR 1.02; 95% CI 0.32 to 3.24
Number of patients with ≥1 hospitalisations (all cause)	OR 0.91; 95% CI 0.53 to 1.58
Number of patients with ≥1 hospitalisations due to exacerbations	OR 0.63; 95% CI 0.34 to 1.17
Pre-dose FEV_1	MD 0.07; 95% CI -0.03 to 0.17
Number of patients suffering ≥1 serious adverse events (non-fatal)	OR 1.02; 95% CI 0.20 to 5.14
Number of patients suffering ≥1 adverse events	OR 1.58; 95% CI 0.93 to 2.68
Total number of patients withdrawn	OR 0.45; 95% CI 0.27 to 0.74
Number of patients withdrawn due to adverse events	OR 1.38; 95% CI 0.47 to 4.09
Number of patients withdrawn due to lack of efficacy	OR 0.36; 95% CI 0.21 to 0.63

HISTORY

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CONTRIBUTIONS OF AUTHORS

Charlotta Karner and Chris Cates included and excluded references, extracted data, assessed study quality and wrote the protocol and the review.

DECLARATIONS OF INTEREST

None known

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INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage]; Adrenergic beta-Agonists [*administration & dosage]; Delayed-Action Preparations [administration & dosage]; Drug Therapy, Combination [methods]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic; Scopolamine Derivatives [*administration & dosage]

MeSH check words

Humans