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[Intervention Review]

Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma

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ABSTRACT

Background

Despite the availability of several evidence-based therapies and non-pharmacological strategies to improve control of symptoms and prevent exacerbations of asthma, patients with asthma continue to be at risk for mortality and morbidity.

Previous trials have demonstrated the potentially beneficial effects of the long-acting muscarinic antagonist (LAMA) tiotropium on lung function in patients with asthma; however, a definitive conclusion on the benefit of LAMA in asthma is lacking, as is information on where in the current step-wise management strategy they would be most beneficial.

Objectives

To assess the efficacy and safety of a LAMA added to any dose of an inhaled corticosteroid (ICS) compared with the same dose of ICS alone for adults whose asthma is not well controlled.

Search methods

We searched the Cochrane Airways Group Specialised Register (CAGR) from inception to April 2015, and we imposed no restriction on language of publication. We also searched clinicaltrials.gov, the World Health Organization (WHO) trials portal and drug company registries to identify unpublished studies.

Selection criteria

We searched for parallel and cross-over randomised controlled trials in which adults whose asthma was not well controlled by ICS alone were randomly assigned to receive LAMA add-on or placebo (both combined with ICS) for at least 12 weeks.

Data collection and analysis

Two review authors independently screened the searches and extracted data from study reports. We used Covidence for duplicate screening, extraction of study characteristics and numerical data and risk of bias ratings. Pre-specified primary outcomes included exacerbations requiring oral corticosteroids, quality of life and all-cause serious adverse events.

Main results

We identified five studies that met the inclusion criteria. All studies applied a double-blind, double-dummy design, and the population of all studies totalled 2563 adult participants. Study duration ranged from 12 weeks to 52 weeks, and risk of bias across domains in all studies was low. Trials included more women than men (33% to 47% male), and mean age of participants ranged from 41 to 48 years. Participants generally had a long history of asthma, and mean baseline predicted forced expiratory volume in one second (FEV_1) was between 72% and 75% in three studies reporting pre-bronchodilator values.

The rate of exacerbations requiring oral corticosteroids (OCS) was lower in patients prescribed an LAMA add-on than in those receiving the same dose of ICS alone (odds ratio (OR) 0.65, 95% confidence interval (CI) 0.46 to 0.93; 2277 participants; four studies; I^2 = 0%; high-quality evidence), meaning that 27 fewer people per 1000 would have an exacerbation over 21 weeks requiring OCS with LAMA compared with ICS alone (95% CI 42 fewer to 6 fewer).

All-cause serious adverse events (SAEs) and exacerbations requiring hospital admission were rare and the effects too imprecise to permit firm conclusions, but effects suggested that LAMA add-on may be associated with fewer of both compared with ICS alone (SAEs: OR 0.60, 95% CI 0.23 to 1.57; 2532 participants; four studies; low-quality evidence; exacerbations requiring hospital admission: OR 0.42, 95% CI 0.12 to 1.47; 2562 participants; five studies; moderate-quality evidence). Additional therapy with a LAMA showed no clear benefit in terms of quality of life compared with ICS given alone; high-quality evidence showed only a small mean improvement in quality of life as measured on the Asthma Quality of Life Questionnaire (AQLQ), which was not statistically significant. The same was true for asthma control as measured on the Asthma Control Questionnaire (ACQ), which was based on moderate-quality evidence. LAMA combined with ICS showed consistent benefit in a range of lung function measures compared with the same dose of ICS alone, and LAMA was not associated with significantly higher rates of adverse events than were reported with placebo.

Authors' conclusions

For adults taking ICS for asthma without a long-acting beta$_2$ -agonist (LABA), LAMA given as add-on treatment reduces the likelihood of exacerbations requiring treatment with OCS and improves lung function. The benefits of LAMA combined with ICS for hospital admissions, all-cause serious adverse events, quality of life and asthma control remain unknown.

Results of this review, along with findings of related reviews conducted to assess the use of LAMA in other clinical scenarios involving asthma, can help to define the role of LAMA in the management of asthma. Trials of longer duration (up to 52 weeks) would provide a better opportunity to observe rare events such as serious adverse events and exacerbations requiring hospital admission.

PLAIN LANGUAGE SUMMARY

Does adding a long-acting muscarinic antagonist (LAMA) to an inhaled steroid help people with uncontrolled asthma more than an inhaled steroid alone?

Main point: People with poorly controlled asthma are less likely to have an asthma attack needing treatment with oral steroids if they take a LAMA on top of their inhaled steroid. LAMA also improve lung function compared with inhaled steroids alone, but their benefit is uncertain for hospital admissions, serious adverse events, quality of life and asthma control.

Why is this question important?

Although lots of medicines are available to treat people with asthma, some patients remain at risk of dying when their disease is poorly controlled. A class of inhaled drugs called long-acting beta$_2$-agonists (LABA) are usually given as an add-on to people whose asthma is not well controlled by inhaled steroids alone, and long-acting muscarinic antagonists (LAMA) are newer drugs now considered as an alternative add-on for these patients.

How did we answer the question?

We looked for randomised controlled studies of at least 12 weeks that compared LAMA as an add-on to inhaled steroids versus inhaled steroids alone. Two people searched through databases and websites, looked at all published and unpublished studies, and compiled a list of studies that looked at the review question. The most recent searches were done in April 2015.

What did we find out?

Over five months, fewer people using a LAMA required oral steroids for an asthma attack, and their lung function was improved over that of patients taking inhaled steroids alone. It looked as though people taking LAMA might be less likely to have to go to the hospital for an asthma attack or for another 'serious adverse event', but we couldn't be sure because the studies were short, and these things did not happen very often in either group. A LAMA added to an inhaled steroid did not appear to improve people's quality of life or control of asthma symptoms.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

LAMA add-on compared with ICS alone for adults with asthma

Patient or population: adults with asthma not well controlled on ICS alone
Settings: out-patient
Intervention: LAMA add-on
Comparison: ICS alone
Time point: weighted mean duration of the studies included in each analysis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ICS alone	LAMA add-on				
Exacerbations requiring oral corticosteroids (OCS) **21 weeks**	80 per 1000	53 per 1000 (38 to 74)	**OR 0.65** (0.46 to 0.93)	2277 (4 RCTs)†	⊕⊕⊕⊕ High	LAMA benefit
Quality of life (AQLQ) 1 = severely impaired; 7 = not impaired at all **23 weeks**	Mean AQLQ score in the control group was 5.44	Mean AQLQ score in the intervention group was 0.05 better (0.03 worse to 0.12 better)	-	1713 (3 RCTs)	⊕⊕⊕⊕ High[a]	MCID = 0.5
All-cause serious adverse events **24 weeks**	29 per 1000	18 per 1000 (7 to 45)	**OR 0.60** (0.23 to 1.57)	2562 (5 RCTs)	⊕⊕◯◯ Low[b,c]	
Exacerbations requiring hospital admission **24 weeks**	6 per 1000	2 per 1000 (1 to 9)	**OR 0.42** (0.12 to 1.47)	2562 (5 RCTs)	⊕⊕⊕◯ Moderate[c]	

Lung function - trough FEV_1 (L, change from baseline) **24 weeks**	Mean change in trough FEV_1 in the control group was -0.02 L	Mean trough FEV_1 in the intervention group was 0.14 higher (0.10 higher to 0.17 higher)	-	2459 (5 RCTs)	⊕⊕⊕⊕ High[c,d]	
Asthma control (ACQ) 0 = no impairment; 6 = maximum impairment **21 weeks**	Mean ACQ total in the control group was 1.47	Mean ACQ total in the intervention group was 0.08 better (0.19 better to 0.03 worse)	-	1916 (3 RCTs)	⊕⊕⊕◯ Moderate[a,e]	MCID = 0.5
Any adverse events **24 weeks**	506 per 1000	493 per 1000 (450 to 539)	**OR 0.95** (0.80 to 1.14)	2562 (5 RCTs)	⊕⊕◯◯ Low[c,f]	

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
†Only pooled data from the twin trials were available for this outcome and had to be entered under one study ID.
ACQ: Asthma Control Questionnaire; **AEs:** adverse events; **AQLQ:** Asthma Quality of Life Questionnaire; **CI:** confidence interval; **FEV_1:** forced expiratory volume in 1 second; **ICS:** inhaled corticosteroid; **LAMA:** long-acting muscarinic antagonist; **MCID:** minimal clinically important difference; **OCS:** oral corticosteroid.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Confidence interval does not exclude the possibility of benefit from ICS alone, but both confidence limits are well below the established MCID of 0.5 on these scales (no downgrade).
[b] I^2 = 59%, P value = 0.05 (-1 inconsistency).
[c] One study in this analysis allowed participants to continue taking combination ICS/LABA; therefore, some results were derived from participants who do not meet all inclusion criteria for this review. The study accounted for a maximum of 26.7% of the analysis weight, and mostly less than 20% (-1 indirectness).
[d] Some statistical heterogeneity but not statistically significant (no downgrade).
[e] I^2 = 72%, P value = 0.03 (-1 inconsistency).
[f] Some studies reported "adverse events (all)" as those not classed as serious; therefore, this figure taken alone may not equal adverse events of all severities. In addition, it was sometimes possible to extract adverse event (AE) data from clinicaltrials.gov only when AEs occurring in > 5% of participants were listed (-1 indirectness).

BACKGROUND

Description of the condition

Asthma is a "heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation" (GINA 2014b). Common triggers include allergens, pollutants and viral infections, although endogenous factors have also been identified. The World Health Organization (WHO) recognises the global burden of asthma and estimates a worldwide prevalence of 300 million people of all ages, with 250,000 people dying each year (WHO 2007). Asthma prevalence is greater in urbanised communities, and with the world's urbanised population projected to grow from 45% to 59% by 2025, the number of people diagnosed with asthma is predicted to increase by 100 million over this time (Global Burden of Asthma Report 2004). Epidemiological data suggest that prevalence is greatest in the developed world, with prevalence amongst adults at 8.2% in the USA (CDC 2014) and at 9% to 10% in the UK (DOH 2012). Asthma presents a heavy financial burden on health services in the UK and worldwide (Global Asthma Report 2011), with the National Health Service (NHS) spending a billion pounds per year on treatment of patients with asthma (Asthma UK 2014). This considerable expense represents direct medical costs, such as provision of medicines and frequent general practitioner (GP) consultations, outpatient services and hospital admissions due to poorly controlled disease (Barnes 1996). However, the economic cost of asthma is worsened by indirect costs to the patient resulting from time off work or school due to sickness and loss of earnings due to morbidity and early mortality (Global Burden of Asthma Report 2004).

Asthma can present with varying degrees of severity; in the most severe cases, it can cause daily chronic symptoms and frequent exacerbations (defined as acute worsening of asthma symptoms). Overarching principles of treatment focus on controlling daily symptoms and preventing exacerbations.

Bronchodilating agents and corticosteroids delivered via inhaler devices are the mainstay in asthma management. Short-acting bronchodilating agents such as salbutamol are used on a "when required" basis as reliever therapy, and inhaled corticosteroids (ICSs) are given regularly as maintenance therapy. Other agents employed in asthma management include inhaled long-acting bronchodilating beta$_2$-agonists (LABA) and leukotriene-receptor antagonists (taken as tablets). Treatment is introduced and is increased through a step-wise approach, depending on the severity and frequency of symptoms (BTS/SIGN 2012; GINA 2014a).

Description of the intervention

Asthma treatment is commenced at the level most likely to achieve control of the patient's symptoms; treatment is stepped up to maintain this control and is stepped down when the patient's condition is stable and has been well maintained (BTS/SIGN 2012; GINA 2014a). Step 1 involves the use of a short-acting bronchodilating agent alone on a when-required basis; patients who remain inadequately controlled are increased to step 2, with the introduction of an inhaled corticosteroid (ICS) for regular use as maintenance therapy. Regular daily therapy with an ICS is known to improve lung function and symptom control while reducing airway inflammation and use of reliever therapy compared with intermittent use of an ICS (Chauhan 2013). However, if regular use of an ICS at a low to medium dose does not maintain control of the patient's symptoms-that is, the patient suffers from recurrent exacerbations or nocturnal awakening, or frequently uses reliever therapy to relieve symptoms of breathlessness, chest tightness and wheeze-a step up in treatment to step 3 is required. At step 3 in the management guidelines, the addition of a long-acting beta$_2$-agonist (LABA) is recommended for adults, as this was found to be superior to alternative treatments (Chauhan 2014: Ducharme 2010). Alternative therapies for people whose asthma is not well controlled on low to medium doses of ICS and for whom a LABA has not worked include introducing a daily leukotriene receptor antagonist tablet or increasing the ICS dose (BTS/SIGN 2012; GINA 2014a).

Long-acting muscarinic antagonists (LAMAs) are not currently recommended in evidence-based guidelines for the treatment of patients with asthma; only one LAMA preparation (Spiriva Respimat 2.5 mcg) has had its licence extended for use in people with asthma, and only for patients already taking combination LABA and ICS who have had at least one severe exacerbation in the previous year (eMC 2014a). However, several other LAMA preparations are used frequently for the treatment of chronic obstructive pulmonary disease (COPD). COPD, like asthma, is characterised in part by airway obstruction, and patients benefit from the bronchodilating effects of LAMA, which reduce airflow limitation and improve symptoms (NICE 2010). Previous studies have demonstrated that the LAMA tiotropium significantly reduced the frequency of exacerbations and hospital admissions related to COPD, and improved lung function and quality of life in patients with COPD (Karner 2014).

How the intervention might work

Long-acting muscarinic antagonists act by inhibiting the effects of acetylcholine at muscarinic (M)-receptors. When administered via inhalation, they competitively antagonise M_3-receptors, preventing acetylcholine-mediated constriction of bronchial smooth muscle. This permits dilation of the airways. Their slow dissociation from local M_3-receptors and prolonged half-lives mean that such agents are administered only once or twice daily (EMC 2013a; EMC 2013b; EMC 2014b).

Chronic obstructive pulmonary disease and asthma share similar symptoms, namely, shortness of breath, chronic cough and wheeze (BTS/SIGN 2012; NICE 2010). Regulation of airway smooth muscle tone by M-receptors is enhanced and contributes to airflow obstruction in both COPD and asthma (Gosens 2006). Therefore, a reduction in M-receptor-mediated airway constriction would be beneficial in relieving these common symptoms of COPD and asthma.

Previous studies and national guidelines for COPD have shown that LAMA and LABA have comparable efficacy in treating patients with moderate COPD (NICE 2010). LABA is also a bronchodilator and is the favoured treatment for introduction at step 3 or 4 of asthma management, when it is administered concomitantly with an ICS to improve control of symptoms (GINA 2014a). Although a LAMA mediates bronchial smooth muscle relaxation in a manner different from that of a LABA, its bronchodilatory effect may be beneficial for patients who require a step up in their asthma management when ICS alone is insufficient.

Why it is important to do this review

Although several evidence-based therapies and non-pharmacological strategies are available to improve control of symptoms and to prevent exacerbations of asthma, mortality due to asthma remains a risk for patients. Asthma UK reported 1167 deaths due to asthma in 2011, while "75% of hospital admissions for asthma are avoidable and as many as 90% of the deaths from asthma are preventable" (Asthma UK 2014). This highlights the fact that current management of asthma remains suboptimal and indicates that development of new management strategies and treatments would be beneficial.

As a result of the common features of COPD and asthma-such as up-regulation of M-receptor-mediated airway tone and subsequent symptoms of breathlessness, cough and wheeze-known benefits of inhaled LAMA in COPD may also be beneficial for patients with asthma, particularly those with severe asthma whose condition remains inadequately controlled by current recommended step 3 therapy.

Previous trials have demonstrated the potentially beneficial effects of the LAMA tiotropium on lung function in patients with asthma (Peters 2010; Vogelberg 2014). However, a definitive conclusion on the benefit of LAMA in asthma is lacking, as is information explaining where in the current step-wise management strategy they would be most beneficial. Therefore, a systematic review of all available randomised controlled trials on the addition of a LAMA to an ICS would be beneficial in revealing any benefit to be derived from the use of LAMA in asthma that remains uncontrolled by an ICS alone.

Three associated reviews will assess the following.

- LAMA add-on compared with LABA add-on.
- LAMA add-on compared with increased ICS dose.
- LAMA add-on as triple therapy with LABA + ICS compared with LABA + ICS alone.

OBJECTIVES

To assess the efficacy and safety of a long-acting muscarinic antagonist (LAMA) added to any dose of an inhaled corticosteroid (ICS) compared with the same dose of ICS alone for adults whose asthma is not well controlled.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel and cross-over randomised controlled trials (RCTs) of at least 12 weeks' duration reported as full text, those published as abstract only and those with unpublished data.

We did not exclude studies on the basis of blinding.

Types of participants

We included adults (aged 18 years or older) whose asthma was not well controlled by ICS alone. We excluded trials that included participants with chronic respiratory co-morbidities (e.g. COPD, bronchiectasis).

If studies included adults and adolescents or children younger than 12 years and data are not reported separately, we included them if the mean age in both groups was over 18 years.

Types of interventions

We included trials comparing a LAMA added to any dose of ICS therapy versus continued use of ICS at the same dose. This meant that studies in which participants were randomly assigned to LAMA or placebo, with inclusion criteria specifying that participants should be taking a stable dose of background ICS, were included. We included studies that permitted the use of short-acting medications (e.g. salbutamol, terbutaline, ipratropium) as reliever therapy. We excluded trials in which a LABA was given as part of the randomly assigned treatment and those in which most participants continued their LABA alongside the randomly assigned treatment. Studies involving the addition of any of the following LAMA preparations were included.

- Tiotropium (Spiriva Handihaler or Respimat).
- Aclidinium bromide (Eklira Genuair).
- Glycopyrronium bromide (Seebri Breezhaler).

Types of outcome measures

Primary outcomes

- Exacerbations requiring oral corticosteroids.
- Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire).
- All-cause serious adverse events.

Secondary outcomes

- Exacerbations requiring hospitalisation.
- Lung function (in particular, trough forced expiratory volume in one second (FEV_1)).
- Asthma control (as measured on a validated scale, e.g. Asthma Control Questionnaire, Asthma Control Test).
- Any adverse events.

Reporting by trial authors of one or more of the outcomes listed here was not an inclusion criterion for the review.
If exacerbations were reported as a composite of more than one definition (e.g. study participants with one or more exacerbations requiring hospitalisation or an emergency department (ED) visit), we analysed these separately.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. This Register contains trial reports identified through systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We searched all records in the CAGR using the search strategy provided in Appendix 2.
We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to the present, and we imposed no restriction on language of publication.

Searching other resources

We checked the reference lists of all primary studies and review articles to look for additional references. We searched relevant manufacturers' websites for trials and other information.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) on 9 April 2015.

Data collection and analysis

Selection of studies

Using Covidence, two review authors (DA and KK) independently screened titles and abstracts for inclusion of all potential studies identified as a result of the search. We retrieved the full-text study reports/publications; two review authors (DA and KK) independently screened the full-text reports to identify studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. We will resolve disagreements through discussion or, if required, by consultation with a third person. We identified and excluded duplicates and collated multiple reports on the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and a Characteristics of excluded studies table.

Data extraction and management

We used a data collection form in Covidence that had been piloted on at least one study in the review to document study characteristics and outcome data. Both review authors (DA and KK) extracted the following study characteristics from included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study settings, withdrawals and dates of study.
- Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Interventions: interventions, comparisons, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected and time points reported.
- Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (DA and KK) independently extracted outcome data from included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a useable way, and we resolved disagreements by discussion. One review author (KK) transferred data into the Review Manager (Review Manager 2014 (RevMan)) file. We double-checked that data had been entered correctly by comparing data presented in the systematic review versus those provided in study reports.

Assessment of risk of bias in included studies

Two review authors (DA and KK) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion and assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the Risk of bias in included studies table. We summarised risk of bias judgements across different studies for each of the domains listed and considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). When information on risk of bias was related to unpublished data or correspondence with a trial author, we noted this in the Risk of bias in included studies table.

In cases for which the method of random sequence generation or allocation concealment was not adequately described, but the study was funded by a manufacturer with whom methods had previously been confirmed, we assumed that the same methods were applied. In the event of such insufficient reporting, we contacted the study author or sponsor to ask for additional information to clarify uncertainties and to support our assumption that the same methods were applied.

When considering treatment effects, we took into account the risk of bias for studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios, and continuous data as mean differences or standardised mean differences. We entered presented data as a scale with a consistent direction of effect. We narratively described skewed data reported as medians and interquartile ranges. When both raw data and adjusted analyses (e.g. accounting for baseline differences) were presented, we used the latter. When data published in peer-reviewed papers was different from those given on clinicaltrials.gov, we cross-checked them (using generic inverse vairience (GIV) and RevMan analyses when only mean difference vs placebo was available), and we contacted study sponsor or trial authors to ask for more information if we noted discrepancies in effects.

We undertook meta-analyses only when this was meaningful (i.e. when treatments, participants and the underlying clinical question were similar enough for pooling to make sense).

When multiple trial arms were reported in a single trial, we included only the relevant arms. When two comparisons (e.g. drug A vs placebo and drug B vs placebo) were combined in the same meta-analysis, we halved the control group to avoid double counting.

When both change from baseline and endpoint scores were available for continuous data, we used change from baseline unless most studies reported endpoint scores. If a study reported outcomes at multiple time points, we used the end-of-study measurement.

When both an analysis using only participants who completed the trial and an analysis that imputed data for participants who were randomly assigned but did not provide endpoint data (e.g. last observation carried forward) were available, we used the latter.

For dichotomous outcomes, we assumed equivalence of treatments if the odds ratio estimate and its 95% confidence interval were between the pre-defined arbitrary limits of 0.9 and 1.1.

Unit of analysis issues

For dichotomous outcomes, we used participants rather than events as the unit of analysis (i.e. number of adults admitted to hospital rather than number of admissions per adult).

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as an abstract only). When this was not possible, and when missing data were thought to introduce serious bias, we performed a sensitivity analysis to explore the impact of including such studies in the overall assessment of results**.**

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (e.g. $I^2 > 30\%$), we reported this and explored possible causes through pre-specified subgroup analyses.

Assessment of reporting biases

We were not able to pool more than 10 trials, so we could not examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We used a random-effects model for all analyses, as we expected variation in effects due to differences in study populations and methods. We performed sensitivity analyses using fixed-effect models.

'Summary of findings' table

We created Summary of findings for the main comparison to document all primary and secondary outcomes listed in the protocol. We used the five GRADE (Grades of Recommendation, Assessment, Development and Evaluation) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to the meta-analyses for prespecified outcomes. We applied methods and recommendations as described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software (Brozek 2008). We justified all decisions to downgrade or upgrade the quality of studies by using footnotes and by making comments when necessary to aid the reader's understanding of the review.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses for primary outcomes.

- Duration of therapy (≤ 6 months, > 6 months).
- Corticosteroid dose (according to GINA 2014, defined as low, medium and high cutoffs).
- Dose and type of LAMA (e.g. tiotropium HandiHaler 18 mcg, tiotropium Respimat 5 mcg).

We used the formal test for subgroup interactions provided in Review Manager 2014 (RevMan).

Sensitivity analysis

We planned the following sensitivity analyses on primary outcomes, with the following studies excluded.

- Unpublished data.
- Studies at high risk of bias for blinding (participants and personnel).

We conducted an unplanned sensitivity analysis on primary outcomes by removing one study in which around half of the participants were taking a LABA, which was outside the inclusion criteria.

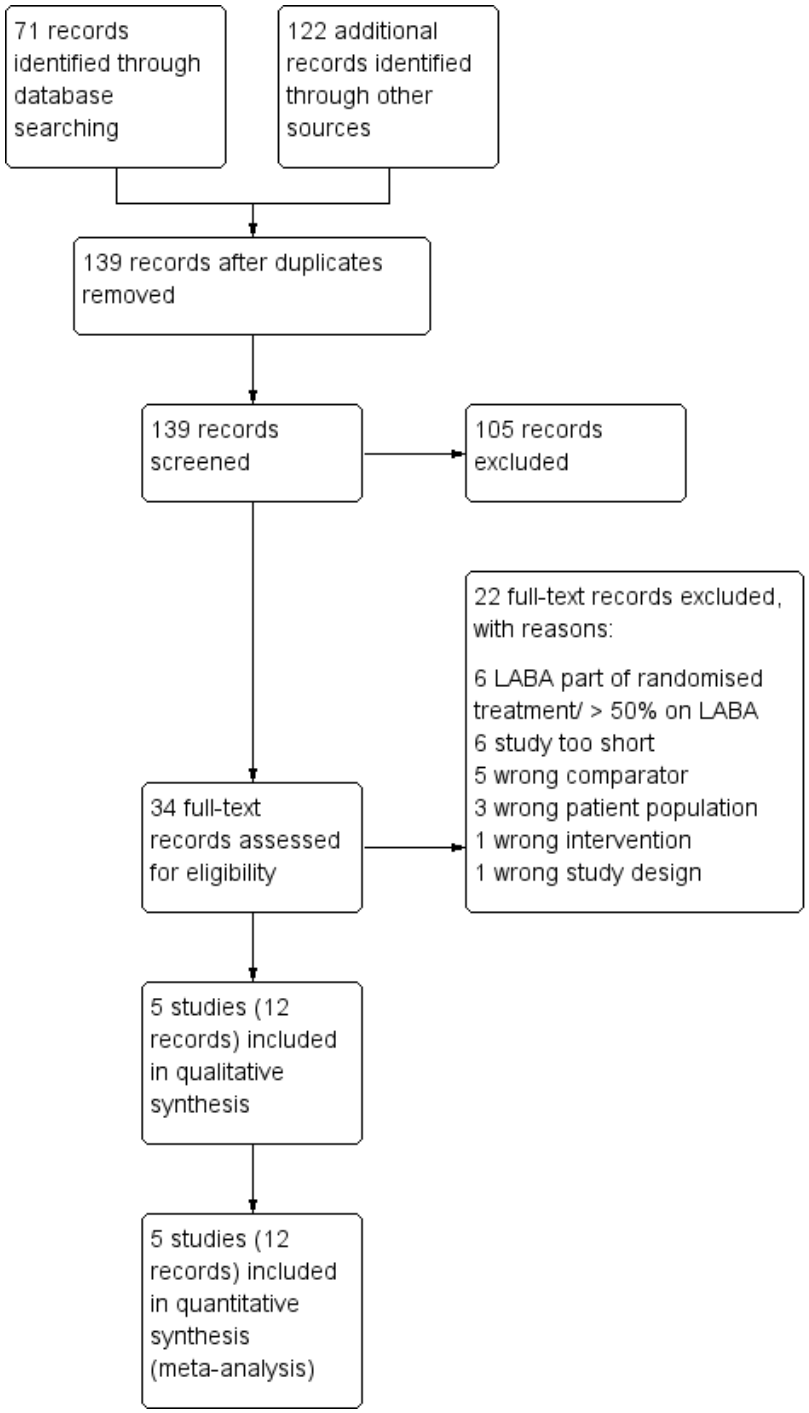
RESULTS

Description of studies

Results of the search

We identified 71 records through electronic database searches and obtained a further 122 records from additional resources (clinicaltrials.gov, reference lists of other publications and drug company trial registries). Of the total 193, we identified 54 as duplicates and screened the remaining 139. Upon screening titles and abstracts, we excluded 105 that did not meet the inclusion criteria. We excluded 22 of the remaining 34 records after retrieving and inspecting full texts; these related to 20 studies. The main reasons for exclusion were as follows: LABA were part of the randomly assigned treatment (n = 6), the study was too short (n = 6) and the wrong comparator was used (n = 5). The remaining 12 records related to five studies that met all inclusion criteria and were included in the qualitative synthesis. All five studies reported data that could be included in at least one meta-analysis. Trial flow is shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

Design and duration

We identified five studies that made the comparison of interest and met the inclusion criteria. Details of study characteristics are provided in Characteristics of included studies and in Table 1. All studies were of a double-blind, double-dummy design, and the population for all studies totalled 2563 adult participants. Duration of studies ranged from 12 weeks to 52 weeks. Only the LAMA plus ICS and placebo (ICS-only) groups in each study are relevant to the present review and are considered herein. The LABA plus ICS groups featured in NCT00350207, NCT01172821 and NCT01172808 are considered in a related systematic review (see Kew 2015). When further clarification of study design or outcome analyses was required, we contacted study authors, who were able to provide additional information and analyses.

Participant inclusion and exclusion criteria

Included participants were between 18 and 75 years of age at the start of the study and had a three-month history of asthma, which was first diagnosed before the age of 40. Included participants were symptomatic despite their current maintenance therapy, which they had been using for at least four weeks before the trials began. Participants included in the studies were able to correctly use all inhaler devices randomly assigned to them and were able to carry out all tests and procedures related to collating outcome measures. Patients with a concomitant "significant disease" were excluded from the study. This was defined by Boehringer Ingelheim as a "disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the trial, or (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial; patients with a clinically relevant abnormal screening (visit 1) haematology or blood chemistry if the abnormality defines a significant disease as defined in exclusion criterion no. 1". Patients with very unstable asthma and requiring in excess of 10 puffs of reliever therapy per day on two consecutive days during the screening period were also excluded from the trials, as were those with concomitant lung disease, arrhythmia or recent history of heart failure or acute coronary disease (within the previous 12 months and 6 months, respectively). Smokers and ex-smokers who had stopped smoking the year before the trial commenced were also excluded from the studies.

Participant baseline characteristics

The mean age of participants and the proportion of males and females in each study group were reported in all five included studies. The mean ages of participants were between 41 and 48 years. The percentage of male participants remained consistently less than half of the study population and ranged from 33.3% to 46.8%.

The mean percentage predicted FEV_1 at baseline was between 72% and 75% in three studies reporting pre-bronchodilator values, and 91% and 94% across groups in the only study reporting post-bronchodilator values (NCT01316380). Participants had a long history of asthma, and the mean number of years since diagnosis ranged from 16 to 23 across groups in the four studies reporting this measure.

Characteristics of the interventions

All of the studies included in this review compared the use of tiotropium in addition to the pre-study ICS medication versus the use of pre-study ICS medication alone. All studies included tiotropium at a dose of 5 mcg daily, and four of the five studies were multi-arm trials that included separate arms receiving 2.5 mcg (low-dose) and 5 mcg (high-dose) of tiotropium daily (NCT01172808; NCT01172821; NCT01316380; NCT01340209). All studies delivered tiotropium via a Respimat inhaler. Matching placebo Respimat inhalers were provided to participants randomly assigned to the placebo group.

Inhaled corticosteroids were not included as part of the randomly assigned treatment but were specified as part of the inclusion criteria of all studies. Inclusion criteria for NCT00350207 included treatment with 400 to 1000 mcg of budesonide or equivalent. One study included only participants with at least a four-week history of treatment with a low, stable dose of ICS (NCT01316380). Remaining studies required at least a four-week history of treatment with a medium, stable dose of ICS (NCT01172808; NCT01172821; NCT01340209). However, in NCT01340209, participants were included if they took ICS alone *or* in fixed combination with a LABA. We included this study because participants were not required to be taking the ICS/LABA combination to be included in the trial, and the split between those taking ICS alone (43%) and those given ICS alongside a LABA (57%) was relatively even. Sensitivity analyses were performed to remove this study from the primary outcomes. Participants in all studies continued this usual maintenance dose of ICS throughout the study period, including those taking LABA alongside ICS in fixed combination in NCT01340209. The actual ICS taken by participants per day was not available in most studies. All studies permitted the use of rescue beta-agonist medication during the study period.

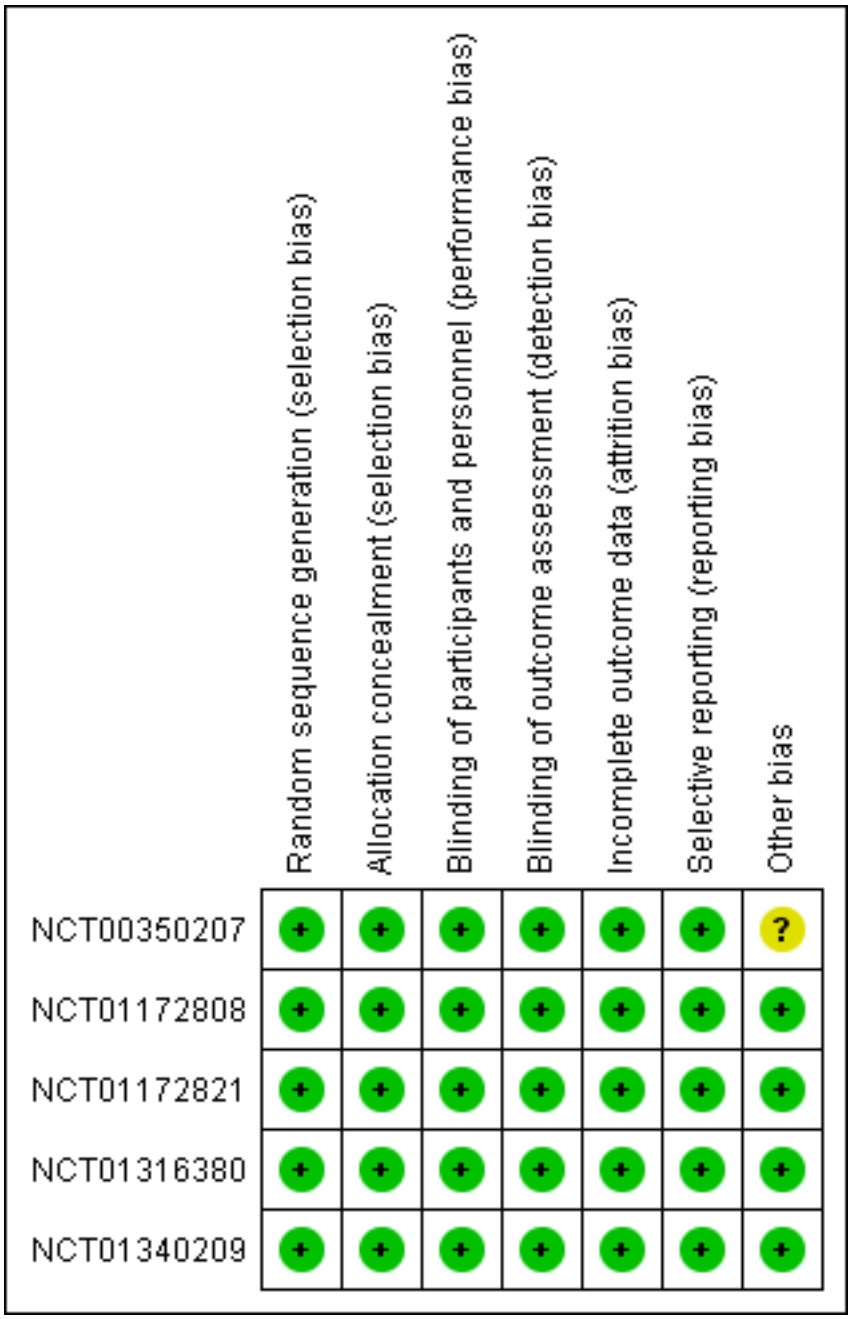
Excluded studies

After viewing full texts, we excluded 13 studies. The main reasons for exclusion included use of a LABA as part of the randomly assigned treatment and the requirement that participants take ICS/LABA combination therapy if they were to be included in the trial (n = 4 records, relevant to a separate review (Kew 2015)). Four records were excluded because they used a comparator not relevant to this review. Other reasons for exclusion were these: study duration too short (i.e. duration < 12 weeks; n = 3 records), wrong intervention used (n = 1 record) and wrong population examined (n = 1 record). Excluded studies and reasons for exclusion are listed in Characteristics of excluded studies.

Risk of bias in included studies

Overall, included studies showed high methodological quality and were largely given low risk of bias ratings (Figure 2). When insufficient information was available in published and publicly available isources, we contacted the trial authors to ask for clarification of methods used.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Information within the clinicaltrials.gov records or published reports was generally insufficient to warrant low risk of bias ratings, but prior contact with study sponsors and additional contact for this review confirmed that standard practices were applied by study sponsors (who used computerised codes and automated allocation systems). For this reason, we judged all included studies to be at low risk of selection bias.

Blinding

We rated all studies as having low risk of bias for blinding of participants, personnel and outcome assessors. All studies were designed to be double-blind and double-dummy, with the use of matching placebo inhalers.

Incomplete outcome data

We rated all studies as having low risk of bias due to attrition. Participant dropout was less than 10% in all groups within the included studies. Investigators reported he numbers of participants who were randomly assigned to a study arm but did not complete the study, as well as the numbers of participants who provided data for all outcome measures. They also provided reasons for non-completion of the study.

Selective reporting

We originally rated two of the included studies as having high risk of bias for selective reporting (NCT01172808, NCT01172821) because the number of participants in each group who had an exacerbation of asthma was not given, even though this was listed as a secondary outcome measure. It was suggested that this was done because "less than 50% of participants in each treatment group experienced an asthma exacerbation". Also in relation to "all adverse events" reported by these two studies, researchers reported only adverse events experienced by at least 5% of the study population, which led to an apparent underestimation of the magnitude of all adverse events experienced. Both of these issues were resolved when the full text was published in a peer-reviewed journal, so we assessed all studies as having low risk of bias for selective reporting.

Other potential sources of bias

We deemed one study to have unclear risk of bias due to another potential source. This involved an imbalance in the number of participants in each study arm who had never smoked and was considered to present potential risk for study outcomes. We noted no issues with the other four studies and consequently rated them as having low risk of bias.

Effects of interventions

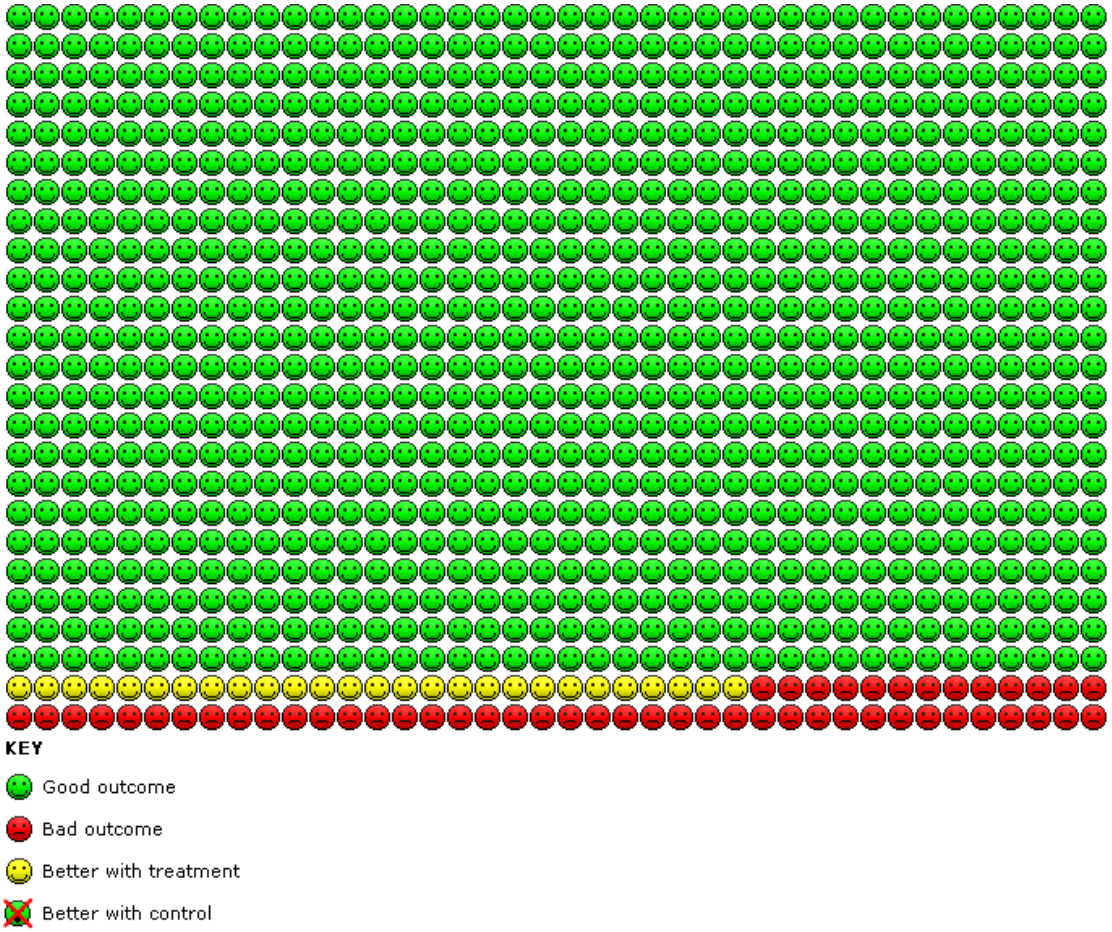
See: **Summary of findings for the main comparison** LAMA add-on compared with ICS alone for adults with asthma

Primary outcomes

Exacerbations requiring oral corticosteroids

LAMA reduced the odds that participants would need to take oral corticosteroids (OCS) for an exacerbation of asthma compared with those for ICS alone (odds ratio (OR) 0.65, 95% confidence interval (CI) 0.46 to 0.93; participants = 2277; four studies; I^2 = 0%). As shown in Figure 3, this means that 27 fewer people per 1000 would require an OCS for an exacerbation longer than 21 weeks if they took a LAMA rather than an ICS alone (95% CI 42 fewer to 6 fewer). Data for the twin trials (NCT01172808 and NCT01172821) were available only as a pooled result, so they had to be entered as one study. We rated the evidence as high quality.

Figure 3. Cates plot showing the absolute effect for the primary outcome.In the control group (ICS alone), 80 out of 1000 people had exacerbations requiring oral corticosteroids over 21 weeks, compared with 53 out of 1000 people for the intervention group (95% CI 38 to 74)(LAMA add-on). As such, in this time period, 27 fewer people taking LAMA add-on would have had an exacerbation requiring oral corticosteroids than if they continued taking ICS alone.



As a supplementary post hoc analysis, we looked at events coded as 'asthma' in the non-serious adverse events tables using MedDRA (Medical Dictionary for Regulatory Activities) terminology.. The sort of asthma events that would have been counted under this term is not clear, so findings are difficult to interpret, but all studies reported data in this way. Fewer 'adverse events classified as asthma' were reported for groups taking LAMA than for those who did not, although the confidence interval showed no difference (OR 0.85, 95% CI 0.69 to 1.05; participants = 2561; five studies; I^2 = 0%). Risk of bias assessments and unpublished data sensitivity analyses were not necessary, but we performed a sensitivity analysis after removing NCT01340209 - the study in which some participants continued to take a long-acting $beta_2$-agonist - and found that results were largely similar (OR 0.87, 95% CI 0.70 to 1.10; participants 2276; four studies; I^2 = 0%). We graded the quality of evidence for this analysis as low after downgrading, because only a small population contributed data to this analysis, only two of the five included studies measured this outcome and poor definitions were provided for exacerbations requiring OCS in each of these studies.

Quality of life

Scores on the Asthma Quality of Life Questionnaire (AQLQ) were slightly higher for those taking a LAMA than for those continuing on ICS alone, but confidence intervals showed benefit for both

treatments and were not within the range of the scale's established minimal clinically important difference (MCID) of 0.5 (MD 0.05, 95% CI -0.03 to 0.12; participants = 1713; three studies; I^2 = 0%). None of the planned sensitivity analyses could be performed on this outcome (no studies at high risk of bias, no unpublished data and no outcomes reported by the partial ICS/LABA study (NCT01340209)). We graded evidence for this outcome as high in quality.

All-cause serious adverse events

People in these studies who were taking LAMA reported fewer serious adverse events, but the pooled effect was too inconsistent and imprecise to suggest a definitive benefit over ICS alone (OR 0.60, 95% CI 0.23 to 1.57; participants = 2562; five studies; I^2 = 59%). Given the heterogeneity, we performed a sensitivity analysis using a fixed-effect model, which increased the precision of the estimate, suggesting fewer serious adverse events in people taking LAMA add-on. As with exacerbations requiring OCS, we performed a sensitivity analysis after removing NCT01340209; the magnitude of the effect was reduced, as was heterogeneity, but it remained similarly imprecise (OR 0.87, 95% CI 0.37 to 2.05; participants = 2277; five studies; I^2 = 27%). This outcome was downgraded to low quality as the result of heterogeneity and inclusion in NCT01340209 of some participants taking a LABA.

Secondary outcomes

Exacerbations requiring hospitalisation

A total of nine people required hospital admission for an asthma exacerbation during study periods, which meant that the estimate was imprecise because few events were reported (OR 0.42, 95% CI 0.12 to 1.47; participants = 2562; five studies; I^2 = 0%). The effect included no benefit due to this imprecision but fewer hospital admissions with LAMA add-on. We also downgraded this outcome because some participants in NCT01340209 did not meet the inclusion criteria.

Lung function

Forced expiratory volume in one second (FEV_1)

Trough FEV_1 measurements improved by an additional 140 mL in people taking LAMA add-on compared with those given ICS alone (mean difference (MD) 0.14 mL, 95% CI 0.10 to 0.17; participants = 2459; five studies; I^2 = 26%). People who had been taking LAMA add-on also had much improved peak FEV_1 measurements (MD 0.19 L, 95% CI 0.15 to 0.23; participants = 1923; three studies; I^2 = 39%). Both analyses showed a degree of inconsistency between study results, but this finding was not statistically significant. We rated the evidence for this outcome as high in quality.

Peak expiratory flow (PEF)

Trough measurement of PEF was almost 30 L/min better in people taking LAMA add-on (MD 28.07 L/min, 95% CI 22.51 to 33.64; participants = 2456; five studies; I^2 = 24%), and again some heterogeneity between study results was evident.

Forced vital capacity (FVC)

People taking a LAMA showed trough FVC improvements 90 mL greater than those found in people not taking a LAMA (MD 0.09, 95% CI 0.05 to 0.13; participants = 2002; four studies; I^2 = 8%), and the result for peak measurements was of similar magnitude and precision (MD 0.11, 95% CI 0.08 to 0.15; participants = 1922; three studies; I^2 = 6%). Both analyses revealed a small amount of statistical heterogeneity.

Asthma control

Participants taking LAMA add-on improved slightly more on the Asthma Control Questionnaire (ACQ) than those taking ICS alone, but confidence intervals for the effect showed no difference and heterogeneity was significant (MD -0.08, 95% CI -0.19 to 0.03; participants = 1916; three studies; I^2 = 72%). Results and confidence intervals also fall well below the scale's MCID of 0.5. We downgraded to moderate the quality of the evidence used to assess differences in ACQ scores because results were inconsistent. The same studies and one other reported the number of people who improved by at least the MCID (ACQ 'responders'). Using this dichotomy, people in the LAMA group were more likely to 'respond' than those taking continued ICS, but the confidence intervals did not rule out the possibility that ICS alone was better, and significant variation between studies was noted (OR 1.23, 95% CI 0.87 to 1.74; participants = 2009; three studies; I^2 = 69%).

Any adverse events

People taking LAMA add-on did not have a significantly different number of adverse events of any kind compared with those given ICS alone (OR 0.95, 95% CI 0.80 to 1.14; participants = 2562; five studies; I^2 = 0%). This outcome was graded as low in quality because some participants were taking LABA in NCT01340209, and because some studies reported only adverse events that occurred in at least 5% of participants.

Subgroup analyses

Duration of therapy

All of the studies reporting exacerbations requiring OCS and the three studies reporting quality of life on the AQLQ were less than six months in duration, so it was not possible to perform a subgroup analysis by duration for these two primary outcomes. These outcomes also showed no important statistical heterogeneity, so it was not necessary to investigate effect modifiers.

A subgroup analysis by study duration for the remaining primary outcome - all-cause serious adverse events - showed a significant difference between the pooled result for the four shorter trials and the one-year-long trial (I^2 = 80%; P value = 0.03). This must be interpreted with caution because of the observational nature of subgroup analyses, and because only one trial was included in one of the subgroups.

Corticosteroid dose

No statistical heterogeneity was noted between studies reporting exacerbations requiring OCS, so comparisons in a steroid dose subgroup analysis were meaningless. The three studies reporting quality of life on the AQLQ used medium doses of inhaled steroids, so no comparison could be made.

We split studies reporting the remaining primary outcome - all-cause serious adverse events - into low-dose (NCT01316380) and medium-dose (NCT00350207; NCT01172808; NCT01172821; NCT01340209) subgroups. NCT00350207 allowed doses up to 1000 mcg budesonide equivalent (high dose), but these were classified as medium dose, as more of the range fell under the medium dose category (400 to 800 mcg). Heterogeneity within the outcome was not accounted for by differences in ICS dose (heterogeneity within the medium-dose subgroup remained significant).

Dose and type of LAMA

All included studies used tiotropium Respimat as their LAMA, and all but one study included two dose groups that were merged in the main comparison. To compare these, we separated out the dose groups and compared them against the same control group, while adjusting for double counting in each analysis. Tests for subgroup differences did not suggest differences between the two doses for any of the primary outcomes (Analysis 2.2).

In addition to the planned subgroup analysis, we performed a direct comparison of the two doses using the four studies in which this was possible (all but NCT00350207). The effect estimate was too imprecise for review authors to conclude whether one dose was better than another for reducing exacerbations requiring OCS (Analysis 3.1). Direct dose comparisons for quality of life on the AQLQ (Analysis 3.2) and for all-cause serious adverse events (Analysis 3.3) did not suggest differences in effect for the two doses.

Sensitivity analyses

Studies at high risk of bias for blinding of participants and personnel

We rated none of the studies as having high risk of bias for blinding.

Unpublished data (i.e. no peer-reviewed full paper available)

No conference abstracts were included, and all data included in the primary outcomes were available in peer-reviewed reports or on publicly available websites.

DISCUSSION

Summary of main results

Five studies met the inclusion criteria; all were double-blind, double-dummy randomised controlled trials and ranged in length from 12 to 52 weeks. We included in this review data from 2563 participants; we conducted this review to compare the use of inhaled corticosteroid (ICS) only versus tiotropium (LAMA) 2.5 mcg or 5 mcg daily in addition to ICS therapy. Participants in all included studies continued their pre-study maintenance dose of ICS throughout the study period, which ranged from low dose to high dose. More women than men were included in the trials (33% to 47% male), and mean age of participants ranged from 41 to 48 years. Participants generally had a long history of asthma, and mean baseline percentage predicted FEV_1 was between 72% and 75% in three studies reporting pre-bronchodilator values. All studies reported good methods and were considered to be at low risk of bias for most of the assessed domains (Figure 2).

High-quality evidence shows that the rate of exacerbations requiring oral corticosteroids (OCS) was significantly lower in patients prescribed a LAMA add-on (27 fewer per 1000 participants, 95% CI 6 fewer to 42 fewer) than in those receiving the same dose of ICS alone.

Similarly, four fewer people per 1000 participants would have an exacerbation resulting in hospitalisation if prescribed a LAMA add-on compared with the same dose of ICS alone; this result was not statistically significant, with a confidence interval ranging from five fewer to three more people (per 1000) having such an exacerbation. Eleven fewer people (per 1000) would experience a serious adverse event when receiving a LAMA add-on; however, the confidence interval ranged from 22 fewer people to 16 more people experiencing a serious adverse event with the addition of LAMA therapy and highlighted the imprecision of this result. Such

events were relatively rare among the study population; this may have been exacerbated by the short study period described in four of the five included studies (< six months).

The addition of LAMA therapy did not show clear benefit for quality of life compared with ICS alone; high-quality evidence of only a small mean increase in quality of life score (AQLQ) was not statistically significant. The same was true for asthma control as measured on the ACQ, which was based on evidence of moderate quality.

Addition of a LAMA led to significant improvement in lung function compared with the same dose of ICS alone, with FEV_1 increased by 0.14 L. Evidence used to evaluate this outcome was graded as high, despite slight heterogeneity and inclusion of data from only one study, which also recruited patients who were using a stable maintenance dose of LABA with ICS and permitted its use throughout the study period. LAMA was not associated with significantly higher rates of adverse events than were reported with placebo.

Overall completeness and applicability of evidence

The evidence base included in this review was lacking in several aspects. All included studies used tiotropium at a dose of 5 mcg daily (licensed dose) or 2.5 mcg daily; therefore, we cannot determine whether the results of this study apply to all other LAMA agents, such as glycopyrronium or aclidinium bromide, which, although not currently indicated for asthma, may be used to treat patients with asthma in the future. Included studies were designed to compare LAMA versus placebo, both combined with the usual ICS dose, but did not detail which ICS participants had used. Therefore, we cannot determine if the results of this study are affected by ICS choice. Study populations included participants using low, medium and high doses of ICS. Therefore, we cannot disregard the fact that this variation in ICS dose may have contributed to observed analyses, although the proportions of particpants using low, medium and high doses of ICS were consistent in both study arms.

All studies included in this review were industry-sponsored trials that were conducted to a very high standard and in a controlled manner. However, this scenario may not truly reflect normal practice, for example, in relation to patient concordance with therapy, which may vary widely in general practice.

This study analysed the effects of LAMA add-on therapy on the frequency of all-cause serious adverse events and exacerbations resulting in hospital admission. Such events were relatively rare in the study populations, and no significant reduction in the frequency of these outcome measures was found. This may reflect inclusion only of patients at step 2 of asthma management (BTS/SIGN 2012), whose disease was not so severe that exacerbations often resulted in hospital admission; however, the low frequency of such events may have been exacerbated by the relatively short duration of the included studies. The benefit of LAMA add-on in reducing all-cause serious adverse events was more pronounced in the only included study lasting longer than six months; therefore, future studies assessing these outcome measures in a similar population would benefit from longer trial duration for more accurate assessment of the effects of LAMA add-on therapy.

Use of LAMA in the management of asthma is relatively new, with only one UK license extension granted for Spiriva Respimat. The licensed indication is only for use as triple therapy for patients already receiving maintenance therapy with a LABA and 800 mcg of budesonide or equivalent, who have had a least one severe exacerbation in the previous year. This group of patients is different from those considered in this review, but the study of LAMA in patients with less severe asthma suggests that further license extensions may be forthcoming. We hope that future versions of this review will provide more powerful and applicable findings on the use of LAMA for patients with less severe asthma.

Quality of the evidence

We rated evidence for one of the primary outcome measures - exacerbations requiring treatment with OCS - as high in quality. Although we included only 137 events in the analysis, we did not consider the effect imprecise, and we included data for more than 2200 people from four multi-centre studies. We rated asthma-related quality of life on the AQLQ as high.

We downgraded evidence for all-cause serious adverse events to low quality as the result of inconsistency and indirectness, the latter because the study (NCT01340209) included participants using an ICS, as well as those using an ICS/LABA in a fixed combination, and did not present results separately for these two groups of patients. Thus, results from participants who did not meet the inclusion criteria for this review have been included and reduce the reliability of the results. This is also true for exacerbations resulting in hospitalisation, lung function and all adverse events.

We downgraded the evidence for asthma control (ACQ total) to moderate because of significant inconsistency.

We downgraded the quality of the analysis of all adverse events to low, in part because of indirectness of the trial, which included some participants taking LABA/ICS, and because some of the included trials were available only on clinicaltrials.gov, which lists only adverse events experienced by a minimum of 5% of the study population.

Potential biases in the review process

We conducted this review in accordance with the standards set by MECIR 2013 and in keeping with the protocol (Allison 2014). We have reported deviations from the protocol in the section titled Differences between protocol and review.

We conducted an additional sensitivity analysis to exclude one trial, which included participants taking a LABA in addition to a stable ICS dose before and during the study period.

As definitions for reported adverse events related to asthma were lacking in these studies, along with details on whether such exacerbations required oral corticosteroids, we conducted an analysis of all adverse events due to asthma.

A skilled information specialist conducted the main electronic searches; thus it is unlikely that any relevant, qualifying studies or trials have been overlooked for inclusion in this review. We supplemented the main searches with searches of other sources (pharmaceutical company clinical trial registries and reference lists of associated studies and reviews), in addition to those required by MECIR 2013 (i.e. clinicaltrials.gov, World Health Organization (WHO) trials portal). We attempted to contact the authors of any trials from which were we required additional data or clarification of methods.

Agreements and disagreements with other studies or reviews

Use of LAMA in the management of asthma has been reviewed in many studies. Timmer et al. found that tiotropium, at doses of 5 mcg daily or 2.5 mcg twice daily, resulted in significant improvement in all measures of lung function compared with placebo, when added to medium-dose ICS for patients with asthma, with a significant increase in adverse events (Timmer 2014). This is consistent with the findings of other studies (Beeh 2014) and systematic reviews, some of which also highlighted the benefit of LAMA added on to other standard asthma treatments, such as ICS/LABA combination therapy, when the disease is inadequately controlled (Befekadu 2014; Rodrigo 2015; Tian 2014). Rodrigo et al. identified that tiotropium add-on to ICS not only significantly improved lung function but also significantly reduced the rate of exacerbations and improved asthma control (Rodrigo 2015).

One study comparing the efficacy of tiotropium versus a LABA found that tiotropium at a dose of 18 mcg daily was comparable with salmeterol at a dose of 50 mcg twice daily when added to medium-dose ICS (Peters 2010). This is consistent with findings of other systematic reviews and a related Cochrane review undertaken to assess the same hypothesis (Kew 2015; Rodrigo 2015).

This evidence supports the use of tiotropium as a bronchodilator in the management of asthma; however, further research is needed to determine the efficacy of other LAMA drugs, and oflong-term treatment, as most available evidence has been provided by studies four to 14 weeks in duration. The results of this review are not consistent with the evidence because these studies were only four weeks in duration, and data may reflect only temporary, short-term improvement in symptoms associated with LAMA use; all studies included in this review have a minimum duration of 12 weeks, and results may highlight the fact that these short-term improvements in disease state are not maintained.

AUTHORS' CONCLUSIONS

Implications for practice

For patients taking ICS without a LABA, LAMA used as add-on therapy reduces the likelihood of exacerbations requiring treatment with OCS and improves lung function. Benefits of LAMA combined with ICS, including hospital admissions, all-cause serious adverse events, quality of life and asthma control, have not been ascertained.

Implications for research

Results of this review, along with those of related reviews assessing the use of LAMA in other clinical scenarios of asthma, will help to define the role of LAMA in the management of asthma. This review should be updated as results from ongoing trials are released. Trials of longer duration would provide better opportunities to observe rare events, such as serious adverse events and exacerbations requiring hospital admission.

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We acknowledge Elizabeth Stovold for designing the search strategy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

NCT00350207

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Open label:** no **Cluster RCT:** no
Participants	**Baseline characteristics** LAMA add-on • *N randomly assigned*: 128 • *N completed*: 120 • *Mean age, years (SD)*: 43.5 (12.6) • *% Male*: 35.9 • *% Predicted FEV_1 (SD)*: 74.1 (16.1) • *% White*: 93.0 • *Duration of asthma, years (SD)*: 18.1 (12.1) ICS alone • *N randomly assigned*: 126 • *N completed*: 119 • *Mean age, years (SD)*: 44.0 (11.9) • *% Male*: 40.5 • *% Predicted FEV_1 (SD)*: 75.3 (19.0) • *% White*: 92.1 • *Duration of asthma, years (SD)*: 17.3 (12.3) **Inclusion criteria:** patients homozygous for arginine at the 16th amino acid position of the $beta_2$-adrenergic receptor (B16 Arg/Arg); informed consent form; male and female out-patients 18 to 65 years of age; documented history of asthma; current non-smokers or ex-smokers with a cigarette smoking history < 10 pack-years; maintenance treatment with inhaled corticosteroids with a total daily dose of 400 to 1000 mcg budesonide or equivalent **Exclusion criteria:** significant disease other than asthma; recent history (i.e. $\leq$ 6 months) of myocardial infarction; hospitalisation for heart failure within the past year; any unstable or life-threatening cardiac arrhythmia, or cardiac arrhythmia requiring intervention or a change in drug therapy within the past year; malignancy for which the patient has undergone resection, radiation therapy or chemotherapy within the past 5 years (treated basal cell carcinoma allowed); COPD; history of life-threatening pulmonary obstruction, cystic fibrosis or bronchiectasis; known active TB; thoracotomy with pulmonary resection; current or recent (6 weeks) pulmonary rehabilitation
Interventions	**Intervention characteristics** LAMA add-on • *ICS type/dose*: 400 to 1000 mcg of budesonide/equivalent • *Add-on type/dose*: tiotropium 2 × 2.5 mcg daily in the evening (with salmeterol-matching placebo twice daily) • *Co-medications*: ICS regimens were maintained throughout the trial. Concomitant respiratory medications were not allowed. Salbutamol metered-dose

	inhaler (MDI) (100 mcg per puff) as needed • *Type of inhaler*: Respimat with MDI placebo • *Duration of treatment*: 16 weeks Placebo (ICS alone) • *ICS type/dose*: 400 to 1000 mcg of budesonide/equivalent • *Co-medications*: ICS regimens were maintained throughout the trial. Concomitant respiratory medications were not allowed. Salbutamol metered-dose inhaler (100 mcg per puff) as needed • *Type of inhaler*: Respimat placebo (and MDI placebo to blind salmeterol arm) • *Duration of treatment*: 16 weeks Participants were also randomly assigned to a third group, salmeterol add-on, which was not relevant to this review
Outcomes	*Continuous* • Trough FEV_1 (L) • Asthma control (ACQ) • Morning PEF (L/min) • Trough FVC (L) • Quality of life (Mini-AQLQ) *Dichotomous* • Any adverse events • All-cause serious adverse events (SAEs) • Exacerbations requiring oral corticosteroids • Exacerbations requiring hospital admission
Identification	**Sponsorship source:** Boehringer Ingelheim, with collaboration from Pfizer **Country:** Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Russia, Slovakia, South Africa, Spain, Turkey, UK **Setting:** 109 investigational sites in 14 countries **Comments:** none **Authors' names:** Leonardo Fabbri (corresponding), Eric D. Bateman (first author) **Institution:** Cape Town, South Africa; Frankfurt and Biberach, Germany; and Modena, Italy **Email:** leonardo.fabbri@unimore.it **Address:** Bateman: Department of Medicine, University of Cape Town; Fabbri: Section of Respiratory Diseases, University of Modena and Reggio Emilia
Notes	**Adverse outcomes:** extracted asthma serious adverse events as 'Exacerbations requiring hospital admission'. On clinicaltrials.gov, SAEs are defined as follows: "Serious Adverse Events include adverse events that result in death, require either inpatient hospitalisation or the prolongation of hospitalisation, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect" Adverse events are defined on clinicaltrials.gov as not including SAEs

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

NCT00350207 (*Continued*)

Random sequence generation (selection bias)	Low risk	At visit 2, participants were randomly assigned (1:1:1 ratio) to placebo, tiotropium or salmeterol. Randomisation was done in blocks of 3 with no stratification. The randomisation schedule was generated by a validated system (PMX CTM Release 3.3. 0 HP2; Propack Data GmbH, Karlsruhe, Germany)
Allocation concealment (selection bias)	Low risk	Reports did not describe whether the randomisation system included a function to conceal the allocation scheme, but prior contact with trial sponsors confirmed the allocation methods used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"blinding was achieved with a double-blind, double-dummy design with matching placebos"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"blinding was achieved with a double-blind, double-dummy design with matching placebos"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was between 4.5% and 6.2% across groups. All but 1 participant (placebo group) were included in the efficacy analyses through imputation
Selective reporting (reporting bias)	Low risk	Outcomes were well reported in the published paper and fully on clinicaltrials.gov
Other bias	Unclear risk	Demographic characteristics were well balanced across treatment groups, with slightly more female patients in the tiotropium group and slightly more patients who had never smoked in the salmeterol group Sponsor and collaborator was Boehringer Ingelheim, manufacturer of the tiotropium inhaler used (Spiriva Respimat)

NCT01172808

Methods	**Study design:** Randomised controlled trial **Study grouping:** parallel group **Open label:** no **Cluster RCT:** no
Participants	**Baseline characteristics** LAMA add-on (low) • *N randomly assigned*: 262 • *N completed*: 249 • *Mean age, years (SD)*: 43.7 (13.1) • *% Male*: 40.5 • *% Predicted FEV_1 (SD)*: 73.1 (8.6) • *% White*: NR • *Duration of asthma, years (SD)*: 22.2 (14.1) LAMA add-on (high) • *N randomly assigned*: 264 • *N completed*: 241 • *Mean age, years (SD)*: 44.4 (12.6) • *% Male*: 41.7 • *% Predicted FEV_1 (SD)*: 72.2 (8.2) • *% White*: NR • *Duration of asthma, years (SD)*: 22.9 (14.7) Placebo (ICS alone) • *N randomly assigned*: 269 • *N completed*: 248 • *Mean age, years (SD)*: 42.5 (13.1) • *% Male*: 38.3 • *% Predicted FEV_1 (SD)*: 73.0 (8.2) • *% White*: NR • *Duration of asthma, years (SD)*: 20.2 (13.4) **Inclusion criteria:** informed consent; males and females 18 to 75 years of age; ≥ 3-month history of asthma at enrolment; diagnosis before 40.5 years of age, confirmed by FEV_1 increase ≥ 12% and ≥ 200 mL after salbutamol; on maintenance treatment with a medium, stable dose of ICS ≥ 4 weeks; ACQ (≥ 1.5) before randomisation; pre-bronchodilator FEV_1 60% to 90% of predicted normal at screening; variation in absolute FEV_1 at screening (pre-bronchodilator) as compared with visit 2 (pre-dose) within ± 30%; non-smoker ≥ 1 year with history < 10 pack-years; ability to use inhalers and perform trial procedures correctly **Exclusion criteria:** lung disease or significant medical illness other than asthma; clinically relevant abnormal screening, haematology or blood chemistry; hospitalisation for cardiac failure during the past year; any unstable or life-threatening cardiac arrhythmia; known active TB; resection, radiation or chemotherapy within 5 years for malignancy (treated basal cell carcinoma allowed); thoracotomy with pulmonary resection; significant alcohol or drug abuse within 2 years; current or recent (6 weeks) pulmonary rehabilitation; known hypersensitivity to study drugs or any other components of delivery systems; pregnant or nursing women; women of childbearing potential not using effective birth control; investigational drug, beta-blockers, tiotropium, oral or patch beta-adrenergics, oral corticosteroids or "experimental" drugs for asthma not recommended by international guidelines within 4 weeks; anti-IgE antibodies, e.g. omalizumab, within

	6 months; cromone, methylxanthines or PDE4 inhibitors within 2 weeks; asthma exacerbation or respiratory tract infection within 4 weeks; previous random assignment in this trial or in the respective twin trial (NCT01172821), or current participation in another trial
Interventions	**Intervention Characteristics** LAMA add-on (low) • *ICS type/dose*: Not part of randomised treatment, participants continued their medium dose of usual ICS • *Add-on type/dose*: Tiotropium 2.5 mcg once daily (evening) • *Comedications*: All, participants were taking maintenance treatment with a medium, stable dose of inhaled corticosteroids for at least 4 weeks prior to Visit 1 • *Type of inhaler*: Respimat (+ HFA MDI placebo twice daily to blind for salmeterol) • *Duration of treatment*: 24 weeks LAMA add-on (high) • *ICS type/dose*: Not part of randomised treatment, participants continued their medium dose of usual ICS • *Add-on type/dose*: Tiotropium 5 mcg once daily (evening) • *Comedications*: All, participants were taking maintenance treatment with a medium, stable dose of inhaled corticosteroids for at least 4 weeks prior to Visit 1 • *Type of inhaler*: Respimat (+ HFA MDI placebo twice daily to blind for salmeterol) • *Duration of treatment*: 24 weeks Placebo (ICS alone) • *ICS type/dose*: not part of randomly assigned treatment; participants continued their medium dose of usual ICS • *Co-medications*: All; participants were taking maintenance treatment with a medium, stable dose of inhaled corticosteroids for ≥ 4 weeks before visit 1 • *Type of inhaler*: Respimat placebo (+ HFA MDI placebo to blind salmeterol arm) • *Duration of treatment*: 24 weeks Participants were also randomly assigned to a fourth group, salmeterol add-on, which was not relevant to this review
Outcomes	*Continuous* • Trough FEV_1 (L, change) • Asthma control (ACQ) • Trough PEF (L/min, change) • Trough FVC (L, change) • Quality of life (AQLQ) • Peak FEV_1 (L, change) • Peak FVC (L, change) *Dichotomous* • Any adverse events • All-cause serious adverse events • Exacerbations requiring hospital admission • Exacerbations requiring oral corticosteroids • Asthma control (ACQ responder)
Identification	**Sponsorship source:** Boehringer Ingelheim **Country:** USA, Brasil, China, Guatemala, India, Japan, Latvia, Mexico, Peru, Poland, Russian Federation

	Setting: 114 Boehringer Ingelheim investigational sites in 11 countries **Comments:** no publications listed; available only on manufacturer's website and clinicaltrials.gov **IDs:** 205.418, NCT01172808 **Author's name:** Boehringer Ingelheim **Institution:** N/A **Email:** clintriage.rdg@boehringer-ingelheim.com **Address:** Boehringer Ingelheim Pharmaceuticals; 1-800-243-0127
Notes	**Pre-treatment:** minimal baseline characteristics reported; no differences noted **TWIN trial with** NCT01172821 **(205.419)**

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote from paper: "Boehringer Ingelheim Pharma GmbH & Co KG (Biberach an der Riss, Germany) generated the randomisation list with a validated pseudo-random number generator and a supplied seed number. The randomisation scheme was generated by the Boehringer Ingelheim randomisation operator at the request of the Boehringer Ingelheim trial statistician"
Allocation concealment (selection bias)	Low risk	Described as 'randomised' on the clinicaltrials.gov record, but no details given. Previous contact with trial sponsors confirmed allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking described as 'double-blind' in the clinicaltrials.gov record From paper: "Patients and study investigators were masked to treatment allocation. Placebo devices were identical in appearance to devices containing active treatments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy, but no specific details about outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was less than 10% in all groups, and the full analysis set was used for all safety and efficacy analyses. "There was 1 patient in the TIO R5 group randomised but not treated" Number allocated to each group was given,

NCT01172808 (*Continued*)

		as well as number completed and number not completed with reasons for non-completion. Also number of participants used was given for each outcome
Selective reporting (reporting bias)	Low risk	Study results were reported on clinicaltrials.gov but did not reveal time to first exacerbation, as "less than 50% of patients in each treatment group experienced an asthma exacerbation". Numbers in each group experiencing exacerbations were subsequently reported in a peer-reviewed journal
Other bias	Low risk	None noted

NCT01172821

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Open label:** no **Cluster RCT:** no
Participants	**Baseline characteristics** LAMA add-on (low) • *N randomly assigned*: 257 • *N completed*: 245 • *Mean age, years (SD)*: 43.0 (12.6) • *% Male*: 37.7 • *% Predicted FEV_1 (SD)*: 72.5 (8.0) • *% White*: NR • *Duration of asthma, years (SD)*: 21.9 (14.5) LAMA add-on (high) • *N randomly assigned*: 253 • *N completed*: 240 • *Mean age, years (SD)*: 44.3 (12.7) • *% Male*: 42.3 • *% Predicted FEV_1 (SD)*: 72.2 (8.3) • *% White*: NR • *Duration of asthma, years (SD):* 23.1 (15.3) Placebo (ICS alone) • *N randomly assigned*: 254 • *N completed*: 240 • *Mean age, years (SD)*: 43.0 (13.0) • *% Male*: 42.9 • *% Predicted FEV_1 (SD)*: 73.0 (8.4) • *% White*: NR • *Duration of asthma, years (SD)*: 22.0 (13.9) **Inclusion criteria:** informed consent; males and females 18 to 75 years of age; ≥ 3-

	months history of asthma at enrolment; diagnosis before 40.5 years of age, confirmed by FEV_1 increase ≥ 12% and ≥ 200 mL after salbutamol; on maintenance treatment with a medium, stable dose of ICS ≥ 4 weeks; ACQ (≥ 1.5) before randomisation; pre-bronchodilator FEV_1 60% to 90% of predicted normal at screening; variation in absolute FEV_1 at screening (pre-bronchodilator) as compared with visit 2 (pre-dose) within ± 30%; non-smoker ≥ 1 year and history < 10 pack-years; ability to use inhalers and perform trial procedures correctly **Exclusion criteria:** lung disease or significant medical illness other than asthma; clinically relevant abnormal screening, haematology or blood chemistry; hospitalisation for cardiac failure during the past year; any unstable or life-threatening cardiac arrhythmia; known active TB; resection, radiation or chemotherapy within 5 years for malignancy (treated basal cell carcinoma allowed); thoracotomy with pulmonary resection; significant alcohol or drug abuse within 2 years; current or recent (6 weeks) pulmonary rehabilitation; known hypersensitivity to study drugs or to any other components of delivery systems; pregnant or nursing women; women of childbearing potential not using effective birth control; investigational drug, beta-blockers, tiotropium, oral or patch beta-adrenergics, oral corticosteroids or "experimental" drugs for asthma not recommended by international guidelines within 4 weeks; anti-IgE antibodies, e.g. omalizumab within 6 months; cromone, methylxanthines or PDE4 inhibitors within 2 weeks; asthma exacerbation or respiratory tract infection within 4 weeks; previous random assignment in this trial or in the respective twin trial (NCT01172808), or current participation in another trial
Interventions	**Intervention characteristics** LAMA add-on (low) • *ICS type/dose*: maintenance treatment with a medium, stable dose of inhaled corticosteroids • *Add-on type/dose*: tiotropium Respimat 2.5 mcg once daily • *Co-medications*: LABAs, other anticholinergics, cromone, methylxanthines and anti-IgE were not permitted. Continuation with other pre-study maintenance therapy and rescue salbutamol was permitted • *Type of inhaler*: Respimat inhaler (+ inhalation of placebo HFA MDI twice daily) • *Duration of treatment*: 24 weeks LAMA add-on (high) • *ICS type/dose*: maintenance treatment with a medium, stable dose of inhaled corticosteroids • *Add-on type/dose*: tiotropium Respimat 5 mcg once daily • *Co-medications*: LABAs, other anticholinergics, cromone, methylxanthines and anti-IgE were not permitted. Continuation with other pre-study maintenance therapy and rescue salbutamol was permitted • *Type of inhaler*: Respimat inhaler (+ inhalation of placebo HFA MDI twice daily) • *Duration of treatment*: 24 weeks Placebo (ICS alone) • *ICS type/dose*: maintenance treatment with a medium, stable dose of inhaled corticosteroids • *Co-medications*: LABAs, other anticholinergics, cromone, methylxanthines and anti-IgE were not permitted. Continuation with other pre-study maintenance therapy and rescue salbutamol was permitted • *Type of inhaler*: Respimat placebo (+ HFA MDI placebo to blind salmeterol arm) • *Duration of treatment*: 24 weeks

NCT01172821 (*Continued*)

	Participants were also randomly assigned to a fourth group, salmeterol add-on, which was not relevant to this review
Outcomes	*Continuous* • Trough FEV_1 (L, change) • Asthma control (ACQ) • Trough PEF (L/min, change) • Trough FVC (L, change) • Quality of life (AQLQ) • Peak FEV_1 (L, change) • Peak FVC (L, change) *Dichotomous* • Any adverse events • All-cause serious adverse events • Exacerbations requiring oral corticosteroids • Exacerbations requiring hospital admission • Asthma control (ACQ responder)
Identification	**Sponsorship source:** Boehringer Ingelheim, with collaboration from Pfizer **Country:** USA, Brasil, China, Guatemala, India, Japan, Latvia, Mexico, Peru, Poland, Russian Federation **Setting:** 125 investigational sites in 11 countries **IDs:** 205.419, NCT01172821 **Author's name:** Thomas B. Casale **Institution:** University of South Florida **Email:** casalej@ceighton.edu **Address:** Morsani College of Medicine, Tampa, FL
Notes	**TWIN trial with** NCT01172808 **(205.418)**

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote from paper: "Boehringer Ingelheim Pharma GmbH & Co KG (Biberach an der Riss, Germany) generated the randomisation list with a validated pseudo-random number generator and a supplied seed number. The randomisation scheme was generated by the Boehringer Ingelheim randomisation operator at the request of the Boehringer Ingelheim trial statistician"
Allocation concealment (selection bias)	Low risk	Previous contact with trial sponsors confirmed allocation concealment methods used

NCT01172821 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind with detailed double-dummy placebo procedure on clinicaltrials.gov From paper: "Patients and study investigators were masked to treatment allocation. Placebo devices were identical in appearance to devices containing active treatments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind with detailed double-dummy placebo procedure on clinicaltrials.gov
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There was 1 patient in the TIO R2.5 and 1 patient in the TIO R5 group randomised but not treated." Dropout ranged between 4.7 and 6.4 across groups, and 99.8% were included by imputation for the full analysis set (FAS) Number of participants allocated to each arm of the study at the start of the study is given, as well as the number who completed it. The number of participants who dropped out is given, as is the reason for non-completion of the trial. The number of participants included in the assessment of each outcome is also given
Selective reporting (reporting bias)	Low risk	Study results were reported on clinicaltrials.gov, but not time to first exacerbation, as "less than 50% of patients in each treatment group experienced an asthma exacerbation". Numbers in each group experiencing exacerbations was subsequently reported in a peer-reviewed journal
Other bias	Low risk	None noted

NCT01316380

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Open label:** no **Cluster RCT:** no
Participants	**Baseline characteristics** LAMA add-on (low) • *N randomly assigned*: 154

	• *N completed*: 149 • *Mean age, years (SD)*: 43.8 (14.0) • *% Male*: 46.75 • *% Predicted FEV_1 (SD)*: 91.3 (post BD) • *% White*: 78.6 • *Duration of asthma, years (SD)*: 17.1 LAMA add-on (high) • *N randomly assigned*: 155 • *N completed*: 152 • *Mean age, years (SD)*: 41.9 (13.0) • *% Male*: 38.06 • *% Predicted FEV_1 (SD)*: 93.2 (post BD) • *% White*: 78.7 • *Duration of asthma, years (SD):* 15.2 Placebo (ICS alone) • *N randomly assigned*: 156 • *N completed*: 154 • *Mean age, years (SD)*: 42.8 (12.1) • *% Male*: 33.55 • *% Predicted FEV_1 (SD)*: 91.5 (post BD) • *% White*: 76.8 • *Duration of asthma, years (SD)*: 16.2 **Inclusion criteria:** informed consent; males and females 18 to 75 years of age; ≥ 3-month history of asthma at enrolment; diagnosis of asthma before 40 years of age; pre-BD FEV_1 60% to 90% predicted normal at visit 1; variation in absolute pre-BD FEV_1 values at visit 1 vs visit 2 within ± 30%; diagnosis of asthma confirmed at visit 1 (or within 2 weeks) with bronchodilator reversibility (within 10 minutes before and 15 to 30 minutes after 400 µg salbutamol/albuterol), resulting in FEV_1 increase of 12% and 200 mL; symptomatic despite low doses of ICS; ACQ ≥ 1.5; low, stable ICS for ≥ 4 weeks before visit 1; never-smokers or ex-smokers ≥ 1 year and smoking history < 10 pack-years; ability to use Respimat inhaler correctly; ability to perform all trial-related procedures, including technically acceptable pulmonary function tests, and to use the e-Diary/peak flow meter (e-Diary-compliance ≥ 80% required); if relevant, continued use of allowed chronic pulmonary medication for entire duration of the study **Exclusion criteria:** lung or additional significant disease other than asthma, requiring more than 10 puffs of rescue medication (salbutamol/albuterol MDI) per 24 hours on 2 consecutive days during the screening period; acute coronary syndrome (STEMI, non-STEMI and unstable angina pectoris) within 6 months; hospitalisation for cardiac failure within 1 year; unstable or life-threatening cardiac arrhythmia, or cardiac arrhythmia requiring intervention or a change in drug therapy within the past year; known active TB; malignancy for which the patient has undergone resection, radiation therapy or chemotherapy within 5 years (treated basal cell carcinoma allowed); thoracotomy with pulmonary resection; significant alcohol or drug abuse within 2 years; current or recent (6 months) pulmonary rehabilitation; known hypersensitivity to anticholinergic drugs, BAC, EDTA or any other components of the tiotropium inhalation solution; pregnant or nursing women; patients of child-bearing potential not using highly effective methods of birth control; treatment with beta-blocker medication, oral or patch beta-adrenergics, systemic, i.e. oral or intravenous corticosteroids, LABA, tiotropium (Spiriva), investiga-

	tional drug, other non-approved/not recommended experimental drugs for asthma (e. g. TNF-alpha blockers, methotrexate, cyclosporin) within 4 weeks before visit 1; topical cardioselective beta-blocker eye medications for non-narrow angle glaucoma allowed; depot corticosteroids within 6 months; ever treated with anti-IgE antibodies; treatment with leukotriene modifiers, systemic anticholinergics, cromolyn sodium or nedocromil sodium and methylxanthines or phosphodiesterase 4 inhibitors within 2 weeks; any asthma exacerbation or any respiratory tract infection within 4 weeks; current participation in another trial
Interventions	**Intervention characteristics** LAMA add-on (low) • *ICS type/dose*: maintenance treatment with a low, stable dose of inhaled corticosteroids • *Add-on type/dose*: tiotropium Respimat 2.5 mcg once daily • *Co-medications*: LABAs, other anticholinergics, leukotriene modifiers, cromone, methylxanthines and anti-IgE were not permitted. Continuation with other pre-study maintenance therapy and rescue salbutamol was permitted • *Type of inhaler*: Respimat inhaler • *Duration of treatment*: 12 weeks LAMA add-on (high) • *ICS type/dose*: maintenance treatment with a low, stable dose of inhaled corticosteroids • *Add-on type/dose*: tiotropium Respimat 5 mcg once daily • *Co-medications*: LABAs, other anticholinergics, leukotriene modifiers, cromone, methylxanthines and anti-IgE were not permitted. Continuation with other pre-study maintenance therapy and rescue salbutamol was permitted. • *Type of inhaler*: Respimat inhaler • *Duration of treatment*: 12 weeks Placebo (ICS alone) • *ICS type/dose*: maintenance treatment with a low, stable dose of inhaled corticosteroids • *Co-medications*: LABAs, other anticholinergics, leukotriene modifiers, cromone, methylxanthines and anti-IgE were not permitted. Continuation with other pre-study maintenance therapy and rescue salbutamol was permitted • *Type of inhaler*: Respimat placebo • *Duration of treatment*: 12 weeks
Outcomes	*Continuous* • Trough FEV_1 (L, change) • Peak FEV_1 (L, change) • Peak FVC (L, change) *Dichotomous* • Any adverse events • All-cause serious adverse events • Exacerbations requiring oral corticosteroids • Exacerbations requiring hospital admission
Identification	**Sponsorship source:** Boehringer Ingelheim, with collaboration from Pfizer **Country:** Argentina, Austria, Croatia, Estonia, Guatemala, Hungary, India, Italy, Korea,

	Republic of, Latvia, Poland, Slovakia **Setting:** 62 Boehringer Ingelheim investigational sites in 12 countries **IDs:** 205.442, 2010-023112-14, NCT01316380 **Authors name:** Professor P. Paggiaro **Institution:** N/A **Email:** clintriage.rdg@boehringer-ingelheim.com; lpaggiaro@dcap.med.unipi.it **Address:** Boehringer Ingelheim Pharmaceuticals; 1-800-243-0127
Notes	None

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	From Boehringer-Ingelheim: "The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system involving a pseudo-random number generator and a supplied seed number, thereby ensuring that the resulting allocation to a treatment is both reproducible and non-predictable"
Allocation concealment (selection bias)	Low risk	From Boehringer-Ingelheim: "An interactive voice response system (IVRS)/ interactive web response system (IWRS) will be used for randomisation to a specific treatment group in this trial and for the appropriate dispensation and supply of medication to patients throughout the trial"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind. Placebo administered in a matching inhaler
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No specific mention of outcome assessors, but described as double-blind. Placebo administered in a matching inhaler
Incomplete outcome data (attrition bias) All outcomes	Low risk	Highest dropout was reported in the tio 2.5 group at 3.2%. Very low across groups, and all outcomes included > 98% of randomly assigned participants. (1) Placebo started = 156, placebo group received 1 dose = 155, placebo completed = 154, participants analysed in each outcome = 154/155. (2) TioR2.5 group started = 154, received at least 1 dose = 154, completed = 149. Par-

NCT01316380 (*Continued*)

		ticipants analysed in each outcome = 149/151/154. (3) TioR5 group started = 155, participants received at least 1 dose = 155, completed = 152, participants analysed for each outcome = 152/155. Reasons for non-completion given
Selective reporting (reporting bias)	Low risk	Results for all outcomes listed in the protocol and on clinicaltrials.gov were uploaded in full as described
Other bias	Low risk	None noted

NCT01340209

Methods	**Study design:** Randomised controlled trial **Study grouping:** parallel group **Open label:** no **Cluster RCT:** no
Participants	**Baseline characteristics** LAMA add-on (low) • *N randomly assigned*: 114 • *N completed*: 106 • *Mean age, years (SD)*: 44.7 (12.1) • *% Male*: 36.84 • *% Predicted FEV_1 (SD)*: NR • *% White*: NR • *Duration of asthma, years (SD)*: NR LAMA add-on (high) • *N randomly assigned*: 114 • *N completed*: 106 • *Mean age, years (SD)*: 42.6 (12.8) • *% Male*: 42.11 • *% Predicted FEV_1 (SD)*: NR • *% White*: NR • *Duration of asthma, years (SD):* NR Placebo (ICS alone) • *N randomly assigned*: 57 • *N completed*: 52 • *Mean age, years (SD)*: 47.8 (13.0) • *% Male*: 33.33 • *% Predicted FEV_1 (SD)*: NR • *% White*: NR • *Duration of asthma, years (SD)*: NR **Inclusion criteria:** informed consent; male and female outpatients 18 to 75 years of age; ≥ 12-week history of asthma at enrolment; diagnosis before 40 years, confirmed by bronchodilator reversibility (15 to 30 minutes after 400 µg salbutamol), resulting in

	FEV_1 increase $\geq$ 12% and $\geq$ 200 mL; on maintenance treatment with a medium, stable dose of ICS (alone or in fixed combination with a LABA) for $\geq$ 4 weeks before visit 1; ACQ $\geq$ 1.5 at screening; pre-bronchodilator FEV_1 60% to 90% of predicted normal at visit 1; never-smokers or ex-smokers $\geq$ 1 year and smoking history < 10 pack-years; ability to use the Respimat inhaler correctly; ability to perform all trial-related procedures **Exclusion criteria:** lung or additional significant disease other than asthma; recent history ($\leq$ 6 months) of myocardial infarction; hospitalisation for cardiac failure within 1 year; any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention, or change in drug therapy within 1 year; known active TB; malignancy and/or resection, radiation therapy or chemotherapy for malignancy within 5 years (treated basal cell carcinoma allowed); undergone thoracotomy with pulmonary resection; significant alcohol or drug abuse within 2 years; known hypersensitivity to anticholinergic drugs, benzalkonium chloride (BAC), ethylenediaminetetraacetic acid (EDTA) or any other components of study medication delivery systems; pregnant or nursing women; women of childbearing potential not using a highly effective method of birth control; use of an investigational drug, beta-blocker, tiotropium (Spiriva), oral beta-adrenergics, systemic corticosteroids, other non-approved/not guideline recommended "experimental" drugs for asthma within 4 weeks before visit 1; topical cardioselective beta-blocker eye medications for non-narrow angle glaucoma allowed; anti-IgE antibodies, e.g. omalizumab (Xolair), within 6 months before visit 1 and/or during the screening period; any asthma exacerbation or any respiratory tract infection in the 4 weeks before visit 1 and/or during the screening period; current participation in another trial; narrow-angle glaucoma and/or micturition disorder due to prostatic hyperplasia; < 80% eDiary completion compliance on visit 2
Interventions	**Intervention characteristics** LAMA add-on (low) • *ICS type/dose*: maintenance treatment with a medium, stable dose of inhaled corticosteroids, with or without LABA • *Add-on type/dose*: tiotropium Respimat 2.5 mcg once daily • *Co-medications*: continuation with pre-study maintenance therapy and rescue salbutamol permitted • *Type of inhaler*: Respimat inhaler • *Duration of treatment*: 52 weeks LAMA add-on (high) • *ICS type/dose*: maintenance treatment with a medium, stable dose of inhaled corticosteroids, with or without LABA • *Add-on type/dose*: tiotropium Respimat 5 mcg once daily • *Co-medications*: continuation with pre-study maintenance therapy and rescue salbutamol permitted • *Type of inhaler*: Respimat inhaler • *Duration of treatment*: 52 weeks Placebo (ICS alone) • *ICS type/dose*: maintenance treatment with a medium, stable dose of inhaled corticosteroids, with or without LABA • *Co-medications*: continuation with pre-study maintenance therapy and rescue salbutamol permitted • *Type of inhaler*: Respimat placebo • *Duration of treatment*: 52 weeks

NCT01340209 (*Continued*)

Outcomes	*Continuous* • Trough FEV_1 (L, change) • Trough PEF (L/min, change) • Trough FVC (L, change) *Dichotomous* • Any adverse events • All-cause serious adverse events • Exacerbations requiring hospital admission
Identification	**Sponsorship source:** Boehringer Ingelheim, with collaboration from Pfizer **Country:** Japan **Setting:** 55 Boehringer Ingelheim investigational sites in Japan **IDs:** NCT01340209; 205.464 **Author's name:** Boehringer Ingelheim **Institution:** N/A **Email:** clintriage.rdg@boehringer-ingelheim.com; **Address:** Boehringer Ingelheim Pharmaceuticals; 1-800-243-0127
Notes	Participants were allowed to continue taking maintenance medication, including LABA. For this reason, the study was removed from the primary outcomes in a sensitivity analysis. 57% of all participants continued to use a LABA during the study period

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as "randomised" on cinicaltrials.gov, wih participants randomly assigned to placebo, LAMA add-on (low dose) and LAMA add-on (high dose) groups at a ratio of 1:2:2, respectively. Prior contact with trial sponsors confirmed that standard procedures included use of computer-generated randomisation codes
Allocation concealment (selection bias)	Low risk	No details given, but prior contact with trial sponsors led to confirmation the adequate measures were taken for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double-blind" on clinicaltrials.gov, with matching inhaler used for placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as "double-blind" on clinicaltrials.gov, with matching inhaler used for placebo

NCT01340209 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Total dropout rate was less than 10% in all groups. "Full analysis set: all patients of the treated set for which baseline and at least 1 post-baseline efficacy measurement were available". This was used for efficacy measures and included > 85% of the randomly assigned population. Numbers who started and completed the study were given, and reasons for discontinuation were stated for those who did not complete the study. Also number of participants analysed per outcome measure is stated
Selective reporting (reporting bias)	Low risk	Data for all pre-specified outcomes were available in full on clinicaltrials.gov
Other bias	Low risk	None noted

ACQ: Asthma Control Questionnaire; AE: adverse event; AQLQ: Asthma Quality of Life Questionnaire; HFA: hydrofluoroalkane; ICS: inhaled corticosteroid; IGE: immunoglobulin E; LABA: long-acting $beta_2$-agonst; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MDI: metered-dose inhaler; NR: not reported; PEF: peak expiratory flow; SAE: serious adverse event; SD: standard deviation.

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

Study	Reason for exclusion
CTRI/2008/091/000306	Too short - single dose of tiotropium Status: not recruiting
CTRI/2012/08/002915	Wrong comparator Status: not recruiting
EUCTR2006-003385-34-NL	Too short Status: authorised
JPRN-UMIN000003618	Wrong participant population (COPD, not asthma) Status: not recruiting
JPRN-UMIN000005459	Wrong participant population (COPD, not asthma) Status: not recruiting
JPRN-UMIN000010352	Too short - single dose of tiotropium Status: not recruiting

(*Continued*)

Kerstjens 2012	LABA included as part of the randomly assigned treatment, or ICS/LABA combination therapy required for inclusion
NCT00546234	Wrong comparator
NCT00557180	Wrong study design - observational Status: not recruiting
NCT00557700	Too short
NCT00706446	Wrong comparator
NCT00772538	LABA included as part of the randomly assigned treatment, or ICS/LABA combination therapy required for inclusion
NCT00776984	LABA included as part of the randomly assigned treatment, or ICS/LABA combination therapy required for inclusion
NCT01290874	Wrong comparator
NCT01573624	Too short
NCT01641692	Too short
NCT01696214	Wrong comparator
NCT02066298	Wrong intervention
NCT02127697	LABA included as part of the randomly assigned treatment, or ICS/LABA combination therapy required for inclusion
Vogelberg 2014	Wrong participant population - adolescents

DATA AND ANALYSES

Comparison 1. LAMA add-on vs ICS alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring oral corticosteroids	3	2277	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.46, 0.93]
2 Quality of life (AQLQ)	3	1713	Mean Difference (IV, Random, 95% CI)	0.05 [-0.03, 0.12]
3 All-cause serious adverse events	5	2562	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.23, 1.57]
4 Exacerbations requiring hospital admission	5	2562	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.12, 1.47]
5 Trough FEV_1 (litres, change from baseline)	5	2459	Mean Difference (IV, Random, 95% CI)	0.14 [0.10, 0.17]
6 Peak FEV_1 (litres, change from baseline)	3	1923	Mean Difference (IV, Random, 95% CI)	0.19 [0.15, 0.23]
7 Trough PEF (litres/min, change from baseline)	5	2456	Mean Difference (IV, Random, 95% CI)	28.07 [22.51, 33.64]
8 Trough FVC (litres, change from baseline)	4	2002	Mean Difference (IV, Random, 95% CI)	0.09 [0.05, 0.13]
9 Peak FVC (litres, change from baseline)	3	1922	Mean Difference (IV, Random, 95% CI)	0.11 [0.08, 0.15]
10 Asthma control (ACQ)	3	1916	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.19, 0.03]
11 Asthma control (ACQ 'responder')	3	2009	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.87, 1.74]
12 Any adverse events	5	2562	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.14]
13 Adverse events classified as asthma	5	2561	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.05]

Comparison 2. Subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause serious adverse events - by study duration	5	2562	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.23, 1.57]
1.1 ≤ 6 months	4	2277	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.37, 2.05]
1.2 > 6 months	1	285	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.07, 0.53]
2 Exacerbations requiring oral corticosteroids - by Respimat dose	3	2277	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.46, 0.93]
2.1 Respimat 2.5 mcg	2	1012	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.29, 0.95]
2.2 Respimat 5 mcg	3	1265	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.48, 1.15]
3 Quality of life (AQLQ) - by Respimat dose	3	1713	Mean Difference (IV, Random, 95% CI)	0.05 [-0.03, 0.12]
3.1 Respimat 2.5 mcg	2	734	Mean Difference (IV, Random, 95% CI)	0.04 [-0.08, 0.16]

3.2 Respimat 5 mcg	3	979	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]
4 All-cause serious adverse events - by Respimat dose	5	2717	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.30, 1.03]
4.1 Respimat 2.5 mcg	5	1487	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.22, 1.50]
4.2 Respimat 5 mcg	4	1230	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.21, 1.43]
5 All-cause serious adverse events - by ICS dose	5	2562	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 1.00]
5.1 Low-dose ICS	1	464	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.03, 8.05]
5.2 Medium-dose ICS	4	2098	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.35, 1.01]

Comparison 3. Respimat 2.5 mcg vs 5 mcg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring oral corticosteroids	2	1345	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.29, 3.14]
2 Quality of life (AQLQ)	2	973	Mean Difference (IV, Random, 95% CI)	0.00 [-0.09, 0.10]
3 All-cause serious adverse events	4	1573	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.50, 2.02]

ADDITIONAL TABLES

Table 1. Summary characteristics of included studies

Study ID	Country	Total N	Duration (weeks)	Blinding	Randomly assigned groups	Age (mean, y)	% pred FEV_1
NCT00350207	International	254	16	DB, DD	1) Tiotropium Respimat 5 mcg daily 2) Placebo (ICS alone)	43.5 44.0	74.1 75.3
NCT01172808	International	795	24	DB, DD	1) Tiotropium Respimat 2.5 mcg daily 2) Tiotropium Respimat 5 mcg daily 3) Placebo (ICS alone)	43.7 44.4 42.5	73.1 72.2 73.0
NCT01172821	International	764	24	DB, DD	1) Tiotropium Respimat 2.5 mcg daily 2) Tiotropium Respimat 5 mcg	43.0 44.3 43.0	72.5 72.2 73.0

Table 1. Summary characteristics of included studies (*Continued*)

					daily 3) Placebo (ICS alone)		
NCT01316380	International	465	12	DB, DD	1) Tiotropium Respimat 2.5 mcg daily 2) Tiotropium Respimat 5 mcg daily 3) Placebo (ICS alone)	43.8 41.9 42.8	91.3* 93.2 91.5
NCT01340209	Japan	285	52	DB, DD	1) Tiotropium Respimat 2.5 mcg daily 2) Tiotropium Respimat 5 mcg daily 3) Placebo (ICS alone)	44.7 42.6 47.8	N/R N/R N/R

Total N is the number randomly assigned to the groups of interest for this review. Age and % predicted FEV_1 are presented as mean values.

DB = double-blind; DD = double-dummy; NR = not reported; OL = open label.

* Values here are post-bronchodilator.

CONTRIBUTIONS OF AUTHORS

Debbie Allison wrote the Background, and Kayleigh Kew wrote the Methods, each with critical input from the other review author. Debbie and Kayleigh extracted data, Kayleigh constructed the analyses and both contributed to preparation of a draft. All review authors provided critical input on the final version of the review.

DECLARATIONS OF INTEREST

Debbie Allison: none known.

Kayleigh Kew: none known.

Anne Boyter: none known.

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Internal sources

- No sources of support supplied

External sources

- National Institute of Health Research, UK.

Evidence to guide care in adults and children with asthma, 13/89/14

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We used Covidence for sifting and extracting study characteristics and outcome data. We were not able to pool more than 10 trials, so we could not prepare a funnel plot to explore possible small-study and publication biases.

We performed an additional sensitivity analysis after excluding the trial in which 57% of participants were taking LABA combined with the study medication.

We analysed data for an additional outcome, 'Adverse events classified as asthma', because the preferred data for 'Exacerbations requiring oral corticosteroids' were not available in most trials.

We included no cross-over studies, but had we found any, we would have analysed data from cross-over trials using generic inverse variance (GIV) and only results derived from paired analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage; adverse effects]; Anti-Asthmatic Agents [*administration & dosage; adverse effects]; Asthma [*drug therapy]; Disease Progression; Drug Therapy, Combination [methods]; Muscarinic Antagonists [*administration & dosage; adverse effects]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male