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Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma (Review)

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[Intervention Review]

Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma

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ABSTRACT

Background

Long-acting muscarinic antagonists (LAMA), a class of drugs with proven effectiveness in chronic obstructive pulmonary disease (COPD), are being considered as an add-on option for adults with asthma whose condition is uncontrolled on inhaled corticosteroids (ICS). It is important to assess the safety and efficacy of LAMA add-on as an alternative to the prolonged use of higher doses of ICS, which are known to cause undesirable side effects in some people.

Objectives

To compare the effects of adding a LAMA to any dose of ICS versus increasing the dose of ICS, for uncontrolled asthma in adults.

Search methods

We searched the Cochrane Airways Group Specialised Register (CAGR) from its inception in 1995 to April 2015, imposing no restriction on language of publication. We also handsearched trial registries, reference lists of primary studies and existing reviews, as well as manufacturers' websites.

Selection criteria

We looked for parallel or cross-over randomised controlled trials lasting at least 12 weeks, in which adults whose asthma was not well controlled on ICS alone were randomised to treatment with LAMA add-on to ICS or with an increased dose of ICS. Trials were excluded if patients were taking long-acting beta$_2$-agonists during the study period.

Data collection and analysis

Two review authors independently screened the searches and extracted data from studies meeting all the inclusion criteria. We used Covidence to manage duplicate screening, data extraction and risk of bias judgements, and to form a consensus where discrepancies arose. We used standard methods expected by The Cochrane Collaboration.

The pre-specified primary outcomes were exacerbations requiring a course of oral corticosteroids (OCS), effects on quality of life and serious adverse events.

Main results

One cross-over randomised controlled trial met the inclusion criteria. The trial was performed in 210 patients with moderate to severe asthma and compared the use of the LAMA tiotropium bromide with double dose beclomethasone (an ICS) using a cross-over design and 14-week treatment periods.

Compared with people taking a double dose of ICS, fewer people taking a LAMA add-on had an exacerbation requiring treatment with OCS (odds ratio (OR) 0.57, 95% confidence interval (CI) 0.22 to 1.43) or an exacerbation resulting in emergency department admission (OR 0.49, 95% CI 0.09 to 2.77), but the confidence intervals for both outcomes did not exclude the possibility that double dose ICS was more effective. Serious adverse events and exacerbations requiring hospitalisation occurred in similarly low numbers of people taking each treatment, but confidence intervals were too wide to suggest that the two treatment options were equivalent.

Asthma-related quality of life was similar in both treatment groups (mean difference (MD) in change from baseline 0.10, 95% CI − 0.07 to 0.27). Those taking LAMA add-on scored slightly better on a scale measuring asthma control than those increasing their ICS dose (MD in change from baseline − 0.18, 95% CI − 0.34 to − 0.02), although the difference was clinically small. Evidence was deemed low quality for both quality of life and asthma control.

There was moderate-quality evidence that participants' trough forced expiratory volume in one second (FEV_1) was 100 mL better when taking LAMA add-on than with increased ICS dose (MD in change from baseline 0.10, 95% CI 0.03 to 0.17).

Authors' conclusions

Only one randomised trial was found, comparing tiotropium add-on to increased dose beclomethasone. Differences between the treatments were too small or imprecise to understand whether adding a LAMA to ICS is safer or more effective than increasing the dose of ICS, and there is a possibility of carry-over effects due to the study's cross-over design. LAMA add-on may lead to more improvement in lung function (FEV_1) than an increased dose of ICS.

The results of this review, alongside pending results from related reviews assessing the use of LAMA against other treatments, will help to define the role of these drugs in asthma management, and this review should be updated as results from future trials emerge. Studies assessing the role of LAMA add-on should be longer and include a double-ICS treatment arm so that the results can be interpreted in the context of the guideline-recommended treatment options that are available to physicians.

PLAIN LANGUAGE SUMMARY

For people with uncontrolled asthma on inhaled steroids, is it better to increase the dose or add a long-acting muscarinic antagonist?

We don't yet know whether adding LAMA to ICS is better or worse than increasing the dose of ICS. It is important that future studies include a treatment group for people given a double dose of ICS, because this is an option for doctors treating people with asthma.

Why is the question important?

Physicians treating patients with asthma that is not adequately controlled by inhaled corticosteroids (ICS) can either increase the dose of steroids or add another type of treatment. One type of drug that can complement ICS are long-acting muscarinic antagonists (LAMAs), which are effective in treating other lung diseases and are starting to become available for treating asthma. Increasing the dose of ICS can cause unwanted side effects such as weakened bones, sleep problems and anxiety, so adding a LAMA to existing doses of ICS may be an effective alternative.

How did we answer the question?

Two people looked for published and unpublished research in several databases and websites to find relevant studies comparing LAMA plus ICS with increased doses of ICS for asthma in adults. We analysed the results available up to April 2015 in this systematic review.

What did we find?

We found one study involving 210 patients with asthma. The trial compared adding tiotropium (a LAMA) to doubling the dose of beclomethasone (a steroid).

In the trial, people taking a combination of the LAMA and ICS were slightly less likely to have an asthma attack needing treatment with oral steroids. Our results suggest that for every 1000 people, 18 fewer in the LAMA group would need these treatments compared

to patients treated with an increased dose of ICS. However, there is a relatively wide margin of error in this estimate, and the actual number of patients on LAMA who might need steroids because of an asthma attack could range from 52 fewer to 26 more people per 1000. Similarly, neither option was more clearly beneficial on any of the following measures: asthma attacks resulting in hospitalisation or admission to the emergency department, serious adverse events, control of asthma or quality of life related to asthma. On the other hand, LAMA plus ICS might improve lung function a bit more than increasing ICS dose.

We didn't have much confidence in the findings because the one included study only looked at one type of LAMA (tiotropium) for a short period of time (14 weeks).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

ICS + LAMA add-on *versus* ICS dose increase for adults with asthma

Patient or population: adults with asthma
Settings: outpatient
Intervention: ICS + LAMA add-on
Comparison: ICS dose increase

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ICS dose increase	ICS + LAMA add-on				
Exacerbations requiring a course of OCS[a] 14 weeks	68 per 1000[b]	40 per 1000 (16 to 94)	OR 0.57 (0.22 to 1.43)	174 (1 RCT)	⊕⊕◯◯ low [c,d]	No clear benefit of one treatment over the other
AQLQ score (Scale 1 to 7, where 1 = severely impaired and 7 = no impairment) 14 weeks	The mean change from baseline in the ICS dose-increase group was 0.15[e]	The mean change from baseline was 0.1 better in the LAMA add-on group (0.07 worse to 0.27 better)	-	(1 RCT)	⊕⊕◯◯ low[c,f]	No clear benefit of one treatment over the other; MCID for AQLQ is 0.5
SAEs (all cause) 14 weeks	17 per 1000[b]	17 per 1000 (3 to 81)	OR 1.00 (0.20 to 5.09)	174 (1 RCT)	⊕⊕◯◯ low[c,d]	No clear benefit of one treatment over the other
Exacerbations requiring hospitalisation 14 weeks	6 per 1000[b]	6 per 1000 (0 to 84)	OR 1.00 (0.06 to 16.24)	174 (1 RCT)	⊕⊕◯◯ low[c,d]	No clear benefit of one treatment over the other
Exacerbations requiring ED visit 14 weeks	23 per 1000[b]	11 per 1000 (2 to 60)	OR 0.49 (0.09 to 2.77)	174 (1 RCT)	⊕⊕◯◯ low[c,d]	No clear benefit of one treatment over the other

FEV_1 pre-albuterol (L)	The change from baseline in the ICS dose-increase group was 0.02 L[e]	The mean change from baseline was 0.1 L better in the LAMA add-on group (0.03 better to 0.17 better)	-	(1 RCT)	⊕⊕⊕◯ moderate[c]	Some benefit of LAMA add-on versus ICS dose increase; MCID not well established
ACQ score Scale = 0 to 6 (0 = no impairment; 6 = maximum impairment) 14 weeks	The change from baseline in the ICS dose-increase group was − 0.03[e]	The mean difference in change from baseline was − 0.18 in the LAMA add-on group (0.34 worse to 0.02 worse)	-	(1 RCT)	⊕⊕◯◯ low[c,f]	Small benefit of LAMA add-on over ICS dose increase; unlikely to be clinically significant (MCID = 0.5)

*The basis for the **assumed risk** (e.g. the 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).
ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** Confidence interval; **ED**: emergency department; **FEV_1** : forced expiratory volume in one second; **ICS**: inhaled corticosteroids; **LAMA**: long-acting muscarinic antagonist; **MCID**: minimal clinically important difference; **OCS**: oral corticosteroids; **OR**: odds ratio; **RCT**: randomised controlled trial; **SAE**: serious adverse event.

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]Analyses included one participant who received systemic intravenous corticosteroids only.
[b]Assumed risk for dichotomous outcomes was based on the mean number of endpoint events in the ICS dose increase group (additional data provided by authors).
[c]The included study only examined one drug (tiotropium) in the LAMA class, and compared it with only one type of ICS (beclomethasone). Therefore, we cannot be certain how this evidence relates to other LAMA and ICS drugs. Furthermore, the duration of each treatment period in the single included study was only 14 weeks. Therefore, this limits the likelihood of detecting rare events such as exacerbations and serious adverse events (i.e. the dichotomous outcomes). Overall, each outcome was downgraded one point for indirectness [− 1 indirectness].
[d]Confidence intervals are wide; analysis included data from only one study [− 1 imprecision].
[e]Assumed risk for continuous outcomes was based on the mean change from baseline in the ICS dose increase group (see table 2 in Peters 2010).

[f] The washout period between treatments in the included study may have been insufficient. There was some carryover effect between treatment periods relating to the number of asthma control days (this could influence a patients perception of asthma control and quality of life).

BACKGROUND

Description of the condition

Asthma is a "common and potentially serious chronic disease" that causes difficulty breathing due to narrowing of the airways, thickening of the airway walls and increased mucus production (GINA 2014). Asthma is recognised as a heterogeneous disease, but common symptoms include "wheezing, shortness of breath, chest tightness and cough that vary over time in their occurrence, frequency and intensity" (GINA 2014).

Around the world and particularly in low- and middle-income countries, asthma is frequently undiagnosed and untreated (Global Asthma Report 2014), and it remains a significant cause of avoidable morbidity and mortality in developed countries such as the UK (NRAD 2014), imposing "a substantial burden on patients, their family and the community" (GINA 2014). Recent estimates suggest 334 million people are affected worldwide, with among the highest direct treatment costs and indirect costs of lost productivity for non-communicable diseases (Global Asthma Report 2014). Prevalence estimates vary, and changes over time have been linked to various factors including air pollution, tobacco legislation, diet and prevalence of other atopic diseases (Anderson 2005).

The two broad aims of asthma treatment are to maintain daily symptom control and prevent acute worsening of symptoms known as asthma attacks or 'exacerbations'. To achieve this, medication, usually given via an inhaler, is started at the most appropriate level based on severity and frequency of symptoms, and in accordance with treatment 'steps' laid out in guidelines (e.g. BTS 2014; GINA 2014). Depending on symptom control and frequency of exacerbations after treatment has commenced, therapy can be stepped up by increasing dosage or adding medications to recapture control, or 'stepped down' to maintain patients at the lowest effective level of therapy and minimise side effects.

Description of the intervention

The lowest treatment step for asthma in most guidelines is the sole use of a short-acting bronchodilating inhaler (e.g. salbutamol) on an as-needed basis, which is often sufficient to treat mild or intermittent symptoms. Regular use of low-dose inhaled corticosteroids is the primary recommended preventer therapy for people with persistent asthma that is inadequately controlled with as-needed medication alone (Step 2, BTS 2014; GINA 2014). Regular ICS has been shown to improve lung function and reduce the need for reliever medications (Adams 2008a; Adams 2008b), but some people will continue to have symptoms and asthma attacks. For this group of patients, guidelines suggest a range of treatment options (step 3 and above). Long-acting beta$_2$-agonists (LABA) such as formoterol and salmeterol are the current preferred add-on therapy at step 3 (Ducharme 2008; GINA 2014), as they have been shown to have often small but statistically significant benefits on a range of outcomes over other treatment options such as increasing ICS dose (Ducharme 2010), adding theophylline (Tee 2009), or adding a leukotriene receptor antagonist (Chauhan 2014). Add-on drugs that allow the ICS dose to be kept low are often seen as preferable since prolonged use of higher doses of ICS carries the risk of serious unwanted effects, including growth retardation in children, decreased bone density, eye disorders, sleep problems and anxiety (NICE 2013).

Long-acting muscarinic antagonists (LAMA), a class of drugs with proven effectiveness in chronic obstructive pulmonary disease (COPD) (Karner 2014), are now being considered as another add-on therapy for asthma in adults who require more than ICS alone. Tiotropium, the first and most widely used LAMA to be licenced for COPD , has demonstrated added benefits over LABA in terms of the frequency of exacerbations and hospital admissions for COPD, but not in terms of mortality or overall hospital admissions (Chong 2012). Evidence for the safety and efficacy of aclidinium bromide and glycopyrronium bromide, two LAMA formulations that have recently been licensed for use in COPD, is also emerging (Ni 2014).

How the intervention might work

LAMAs block receptors of the neurotransmitter acetylcholine on airway smooth muscle, glands and nerves, preventing muscle contraction and mucus secretion (Moulton 2011). The action on these receptors helps to alleviate symptoms of breathlessness, coughing and wheezing that characterise asthma (Lipworth 2014). These characteristics of LAMA, together with the overlap in pathophysiology and symptoms between asthma and COPD (Gosens 2006), have led to their testing as an add-on therapy for asthma in patients who do not achieve adequate control from standard-dose ICS alone. This course of treatment has the potential advantage of avoiding prolonged exposure to higher doses of ICS.

The most commonly reported side effect of LAMA for airways disease is dry mouth, with others including constipation, diarrhoea, cough and headache (BNF). All LAMAs for maintenance of airways disease are delivered via inhalers, either by powder (tiotropium bromide, usually delivered via the HandiHaler device; aclidinium bromide, via Genuair; glycopyrronium bromide, via Breezhaler) or soft mist delivery (albuterol and ipratropium combination, via Respimat) and are not suitable to be used as rescue medication.

In COPD, there is conflicting evidence regarding the safety of tiotropium delivered via the Respimat device, with one recent observational study finding it increased the risk of death, particularly cardiac, compared with placebo via the HandiHaler device (Verhamme 2013). Another large randomised trial including over 17,000 people with COPD found no significant differences in long-term safety between the two devices (Wise 2013). As yet it is

unclear whether differential safety profiles will be seen in people with asthma.

Why it is important to do this review

Tiotropium bromide (Spiriva Respimat 2.5 mcg) is the only LAMA preparation that has been granted a UK license for use in severe asthma in combination with LABA and ICS (eMC 2014). Following the demonstrated efficacy of LAMAs in COPD (Karner 2014), clinical trials are emerging to test the use of various LAMA regimens against the existing treatment options for asthma. One study found that nearly 30% of patients whose asthma was uncontrolled on fluticasone remained so with the guideline-recommended addition of LABA (Bateman 2004), suggesting there is a need for more options for add-on therapy.

It is important to assess the safety of using LAMA add-on to ICS as an alternative to prolonged use of high doses of ICS, which are known to cause undesirable side effects (NICE 2013). As a complement to results from three other reviews, this review summarises the evidence to guide the possible use of LAMA add-on as an alternative steroid-sparing agent. The other reviews assess LAMA add-on compared with LABA add-on (Kew 2015), LAMA add-on compared with no change to ICS dose (Allison 2014) and LAMA add-on as part of a triple therapy with LABA+ICS compared with LABA+ICS alone (Kew 2015).

OBJECTIVES

To compare the effects of adding a LAMA to any dose of ICS versus increasing the dose of ICS, for uncontrolled asthma in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included double-blinded parallel or cross-over randomised controlled trials (RCTs) lasting at least 12 weeks. We included studies reported as full-text and those published as abstract only, as well as unpublished data. Because the long-term effects of ICS may not wash out between treatments in cross-over trials, we performed a sensitivity analysis excluding them from the primary analyses.

We did not exclude studies on the basis of a lack of blinding.

Types of participants

We included adults (at least 18 years) whose asthma was not well controlled on ICS alone. We excluded trials that included participants with other chronic respiratory comorbidities (e.g. COPD, bronchiectasis).

If studies also included adolescents or children under 12, and data were not reported separately, we included them if the mean age in both treatment groups was over 18.

Types of interventions

We included studies that randomised participants to receive any dose of the following LAMA preparations as an add-on to any dose of ICS.

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

Eligible comparison group participants were randomised to receive an increase in ICS dose.

We included studies that permitted the use of short-acting medications, such as salbutamol or a combination of terbutaline and ipratropium, as reliever therapy. However, to assess the effect of LAMA plus ICS in isolation, we excluded trials where:

- a long-acting beta$_2$-agonist (LABA) was given as part of the randomised treatment (i.e. LAMA+ICS+LABA vs. ICS+LABA);
- participants were required to be taking a LABA to be included in the trial; and
- the majority of participants continued treatment with LABA alongside the randomised treatment.

Types of outcome measures

Primary outcomes

1. Exacerbations requiring oral corticosteroids
2. Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire)
3. Serious adverse events (all causes)

Secondary outcomes

1. Exacerbations requiring hospitalisation
2. Lung function (in particular, trough FEV$_1$)
3. Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire or Asthma Control Test)
4. Adverse events

Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for the review.

If exacerbations were reported as a composite of more than one definition (e.g. patients with one or more exacerbations requiring hospitalisation or emergency department visit), they were analysed 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. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO as well as through 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 in Appendix 2. The most recent search was conducted in April 2015.

We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to the present, with no restriction on language of publication.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We also searched relevant manufacturers' websites for trial information.

A search was performed on 19 Feburary 2015 for errata or retractions from included full-text studies published on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

The titles and abstracts of all potential studies identified by the search were independently screened for inclusion by two review authors (KK and DE, using Covidence) and coded as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports and publications, and two review authors independently screened these to identify studies for inclusion or to identify and record reasons for the exclusion of the ineligible studies. We resolved any disagreement through discussion, or if required, we consulted a third person (DA or AB). Duplicates were identified and excluded, and multiple reports of the same study were collated so that each study (rather than each report) was the unit of interest in the review. The selection process was recorded in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of included studies' table.

Data extraction and management

We used a data collection form for study characteristics and outcome data, which had been piloted on a related systematic review. Two review authors (DE and KK) extracted the following characteristics from the included study.

1. Methods: study design, total duration of study, details of any run-in period, number of study centres and location, study setting, withdrawals and study period.
2. Participants: Number of patients, mean age, age range, sex, severity and duration of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, duration of intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (KK and DE) independently extracted outcome data from the included study. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Disagreements were resolved by consensus or by involving a third person (DA or AB). One review author (DE) transferred the data into the RevMan file and another author double-checked that data were entered correctly by comparing the data presented in the systematic review with the study report (KK).

Assessment of risk of bias in included studies

Two review authors (DE and KK) independently assessed the risk of bias for the study using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another author (DA or AB). The risk of bias was assessed according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low or unclear and provided a quotation from the study report together with a justification for our judgment in the 'Risk of bias' table. We planned to summarise the risk of bias judgements across different studies for each of the domains listed, but there was only one included study. We considered blinding separately for different key outcomes where 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). Where information on risk of bias

related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.
When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.
We conducted the review according to the published protocol and reported any deviations in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios (ORs) and continuous data as mean difference (MD) or standardised mean difference (SMD). Data presented as a scale were entered with a consistent direction of effect. We provided a narrative description of skewed data reported as medians and interquartile ranges. We analysed data from the cross-over trial using generic inverse variance and only if double-counting of participants was accounted for. If raw data and adjusted analyses (e.g. accounting for baseline differences) were both presented, we used the latter.
If more studies are identified in future updates of this review, we will perform meta-analyses only where meaningful (i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense).
Where multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we halved the control group to avoid double-counting.
If change from baseline and endpoint scores were available for continuous data, we used the change from baseline unless the majority of studies reported endpoint scores. If a study reported outcomes at multiple time-points, we used the end-of-study measurement.
When an analysis using only participants who completed the trial and an analysis which imputed data for participants who were randomised but did not provide endpoint data (e.g. last observation carried forward) were both available, we used the latter.
For dichotomous outcomes, we assumed equivalence of treatments if the odds ratio estimate and its 95% confidence intervals 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). However, if exacerbations were reported as rate ratios we analysed them on this basis. For cross-over trials, we requested data in the format described in Elbourne 2002 to control for intercorrelation of matched pairs. For continuous data in cross-over trials, we entered data using generic inverse variance from suitable adjusted analyses to account for the trial's design.

Dealing with missing data

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

Assessment of heterogeneity

We planned to use the I^2 statistic to measure heterogeneity among the trials in each analysis, report if substantial heterogeneity was identified (e.g. I^2 greater than 30%) and explore possible causes by pre-specified subgroup analysis.

Assessment of reporting biases

We were unable to pool more than 10 trials, so it was not necessary to use a funnel plot to explore possible small study and publication biases.

Data synthesis

We planned to use a random-effects model for all analyses, as we expected variation in effects due to differences in study populations and methods. We planned to perform sensitivity analyses with a fixed-effect model. As only one study met the inclusion criteria for this review, meta-analyses were not performed.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses for the primary outcomes.

1. Duration of therapy (≤ 6 months, > 6 months).
2. Corticosteroid dose in the control group (according to GINA 2014 defined low, medium and high cutoffs).
3. Dose and type of LAMA (e.g. tiotropium Handihaler 18 mcg, tiotropium Respimat 5 mcg).

We planned to use the formal test for subgroup interactions in Review Manager (RevMan).

Sensitivity analysis

We planned to perform sensitivity analyses on the primary outcomes, excluding the following.

1. Unpublished data.
2. Studies at high risk of bias for blinding of participants and personnel.
3. Cross-over studies*.

*There may be longer term effects of ICS that do not wash out before a subsequent treatment is started in cross-over trials, especially at higher doses.

Summary of findings table

We created a 'Summary of findings' table (Summary of findings for the main comparison) to present results for all of the named outcomes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the evidence as it related to the data used to analyse the pre-specified outcomes. We applied methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software (Brozek 2008), justifying all decisions to downgrade or upgrade the quality of studies using footnotes and providing comments to aid the reader's understanding of the review where necessary.

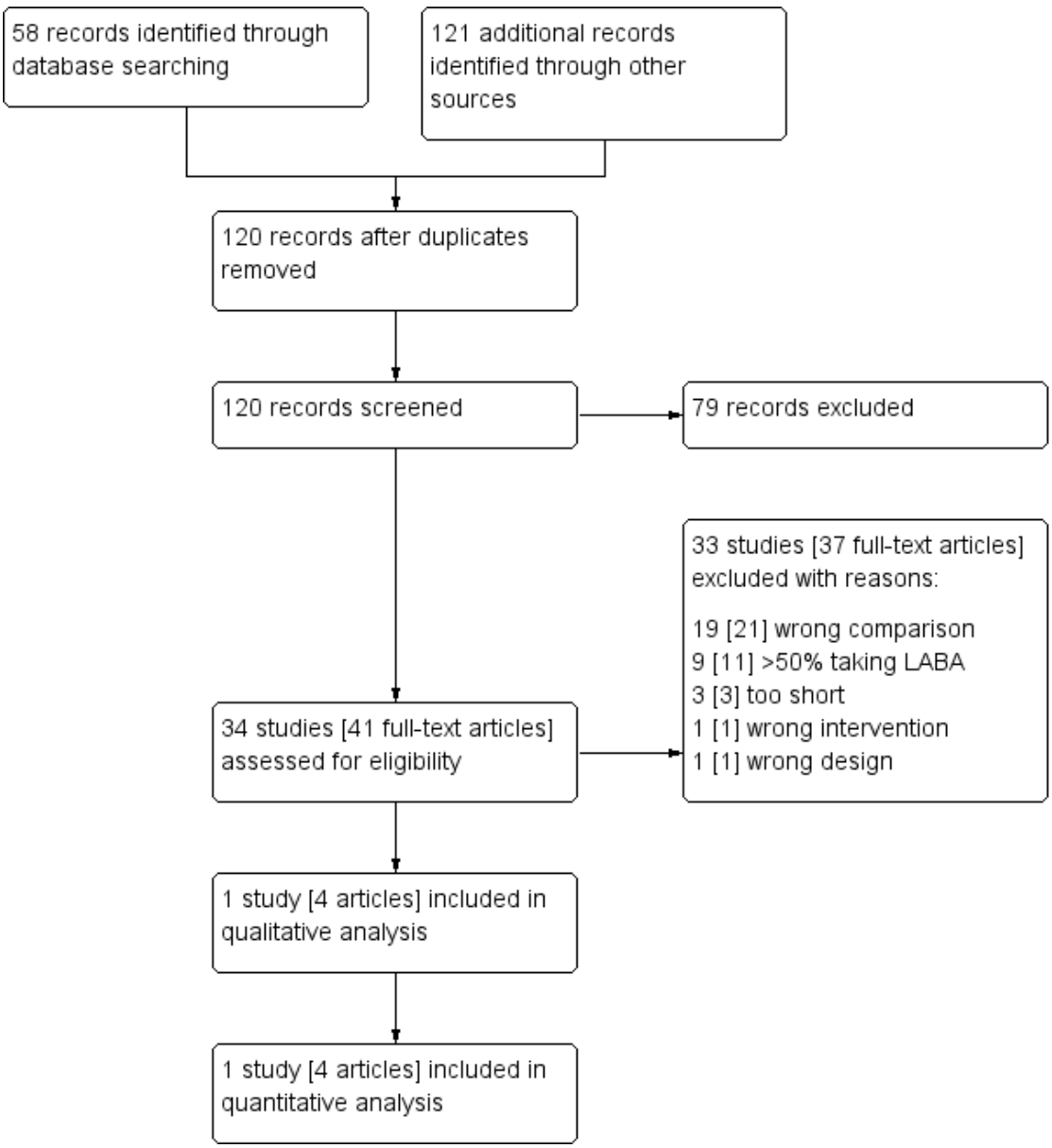
RESULTS

Description of studies

Results of the search

We identified 58 records in the main electronic database searches, and 121 other records by searching additional resources (ClinicalTrials.gov, reference lists of other publications and drug company websites). Fifty-nine of the total 179 records were duplicates. We screened the remaining 120, excluding 79 based on the title and abstract alone. For the remaining 41, we retrieved full texts and grouped them into 34 studies. After viewing them and resolving discrepancies, we excluded 33 studies (37 records), leaving one RCT that met all the inclusion criteria. The reasons for exclusion can be found below in the Excluded studies section. We did not identify any ongoing studies, and no studies are awaiting classification. Trial flow is presented in Figure 1.

Figure 1. Study flow diagram



Included studies

We identified one study making the comparison of interest that met the inclusion criteria (Peters 2010). Details of study characteristics are provided in the 'Characteristics of included studies' table. Briefly, 210 adult participants with asthma received tiotropium bromide (a LAMA) plus beclomethasone (an ICS); salmeterol xinaoate (LABA) plus beclomethasone, or double-dose beclomethasone, in a randomly assigned order (three-way cross-over design). Only the LAMA plus ICS and double ICS groups are relevant to the present review and are considered herein. The comparison between the LAMA plus ICS and LABA plus ICS groups features in a related systematic review (Kew 2015). Participants had moderate to severe asthma that was inadequately controlled by a low-dose ICS (low-dose); patients were symptomatic (i.e. required daily controller therapy). We contacted the authors of the included study, who were able to provide additional information and analyses.

Design

Peters 2010 was a three-way, double-blind, triple-dummy cross-over trial in which patients where randomised to the order in which they received each of the three treatments. The study was performed at multiple centres in the United States, and total study duration was one year, comprising a four-week run-in period followed by three 14-week treatments periods, and separated by two-week washout periods. As mentioned above, only two of the three treatment groups were relevant to this review (see below in 'Characteristics of included studies' table), and data from these treatment groups contributed to the present analyses.

Participants

Inclusion and exclusion criteria are listed in the 'Characteristics of included studies' table. Inclusion criteria included an age of at least 18 years, a history of asthma confirmed by bronchodilator reversibility or bronchial hyperresponsiveness, a FEV_1 of more than 40% of the predicted value, current non-smoking status (with a history of 10 pack-years or less) and no requirement for additional asthma medications. Exclusion criteria included vocal cord dysfunction, respiratory tract infection, other significant medical illness, lung disease other than asthma, an asthma exacerbation within the previous four weeks, a history of life-threatening asthma within the previous five years and pregnancy or no use of acceptable birth control methods in women of childbearing potential.

The majority (67%) of participants were female. The mean (standard deviation, SD) age of participants was 42 (±12) years; mean body mass index was 31.4 (±8.8) kg/m^2 and the mean duration of asthma was 26 (±14.1) years. Mean percentage predicted FEV_1 before bronchodilation was 71.5% (±14.9%) at baseline. The mean (SD) Asthma Control Questionnaire (ACQ) score at baseline was 1.64 (±0.73), which is over the suggested cutoff of 1.50 to be confident of inadequately controlled asthma (Juniper 2006). Baseline Asthma Quality of Life Questionnaire (AQLQ) score was 5.43 (±1.05).

Interventions

The relevant treatment comparison in the included study comprised tiotropium (Spiriva Handihaler; 18 mcg once daily) plus beclomethasone (hydrofluoroalkane metered-dose inhaler; 80 mcg twice daily) versus a dose increase of beclomethasone (160 mcg twice daily; i.e. a double dose of the ICS).

Outcomes

The authors of Peters 2010 provided additional data. Continuous data (mean difference, 95% CI) and dichotomous data (OR, 95% CI) were entered as adjusted between-group differences to account for the trial's cross-over design (Elbourne 2002), so we analysed outcomes using the generic inverse variance method (Higgins 2011).

Excluded studies

We excluded 33 studies after viewing full texts. The main reason for exclusion was use of the wrong comparator (n=21 records), such as ICS alone (relevant to Allison 2014) or ICS plus LABA (Kew 2015). Other reasons for study exclusion included the fact that over 50% of participants were taking LABA (n=11 records), study duration was too short (i.e. less than 12 weeks; n=3 records) or the wrong intervention was used (n=1 record). Likewise, one study was an observational cohort study rather than an RCT(n= 1 record). Excluded studies and reasons for exclusion are listed in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

The included study was of a high methodological quality. Where published and publicly available information was insufficient, the trial authors were able to clarify the methods used.

Allocation

The included study was rated as at low risk of bias for both allocation domains. Communication with trial authors (Chinchilli 2015 [pers comm]) confirmed that a statistical software package was used to generate the random sequence that defined the order

in which treatments would be given. Specifically, a Data Coordinating Centre carried out this task and developed a web-based system to blind allocation. When a patient had completed screening and was ready for randomisation, a study coordinator at a clinical centre entered information into the randomisation module and was notified of the appropriate blinded drug packet (prepared by the network pharmacist) for the eligible patient.

Blinding

The included study had a low risk of bias for both participants and personnel as well as outcome assessor blinding. The three-period cross-over study was designed to be double-blind and triple-dummy with placebo inhalers to blind each of the drugs in each period. The clinical trial register (ClinicalTrials.gov) stated that masking was applicable to subjects, caregivers, investigators and outcome assessors.

Incomplete outcome data

The included study was rated as having a low risk of attrition bias. Less than 10% of patients dropped out during each treatment period. The number of patients withdrawing due to adverse events was lower during treatment with LAMA add-on (n=7) compared with a double dose of ICS (n=14).

Selective reporting

The included study was judged to be at low risk of bias for selective reporting. The outcomes defined in the ClinicalTrials.gov registration were mostly well reported in the published manuscripts, with the exception of the secondary biomarker outcomes, which did not influence the assessment of safety or efficacy. Asthma exacerbations and serious adverse events were not reported in a way that could be analysed without potentially double-counting participants, but the authors were able to provide the missing data.

Other potential sources of bias

Peters 2010 used a cross-over design, and the washout period between treatments was two weeks. This may not have been sufficient, as the authors commented that although minimal carryover effects were observed for measures of lung function, an effect was seen for asthma control days. We considered this to be a potential source of bias.

Effects of interventions

See: **Summary of findings for the main comparison** ICS + LAMA add-on compared to ICS dose increase for adults with asthma

Only one study (Peters 2010) met the inclusion criteria for this review. As such, data from several studies could not be pooled, and no meta-analyses were performed. As the study followed a cross-over design, we obtained additional data from the authors to allow us to calculate between group differences for the dichotomous outcomes. For each dichotomous outcome, the analyses below were based on all patients with complete follow-up or who had an event. The results are described below and presented in Summary of findings for the main comparison.

Primary outcomes

Exacerbations requiring oral corticosteroids

Fewer people taking a LAMA add-on had an exacerbation requiring treatment with oral steroids compared with people taking double dose ICS (OR 0.57, 95% CI 0.22 to 1.43; Analysis 1.1), but the confidence intervals did not exclude the possibility that doubling ICS was better. For people taking LAMA, we estimated that 18 fewer people per 1000 would have an exacerbation requiring steroids, but the confidence intervals ranged from 52 fewer to 26 more people per 1000. The quality of the evidence was rated as low, having been downgraded once for imprecision due to wide confidence intervals and once for indirectness, as our evidence was based on a single study examining only one drug in the LAMA class, and the study lasted only 14 weeks (the results for tiotropium may not be representative of the LAMA class as a group, and the relatively short duration of treatment makes it difficult to interpret the findings for rare events, such as exacerbations or serious adverse events, in the context of long-term use in adults).

Quality of life

People treated with LAMA add-on were not found to have a different quality of life compared with those treated with an increased dose of ICS (MD in change from baseline 0.10, 95% CI − 0.07 to 0.27; Analysis 1.2). The evidence was rated as of low quality after being downgraded once for indirectness (results may not be representative of LAMA as a class of drugs) and once due to risk of bias. We downgraded the evidence based on risk of bias because the washout period between treatments in the included study may have been too short. Indeed, a degree of carryover effect between treatment periods was observed in relation to the number of asthma control days, and this may have influenced patients' perception of quality of life as well as asthma control.

Serious adverse event (all causes)

The confidence intervals were too wide to determine if there was a difference in the number of people who experienced serious adverse events (SAEs) whilst taking a LAMA add-on compared with an increased dose of ICS (OR 1.00, 95% CI 0.20 to 5.09;

Analysis 1.3). The quality of the evidence was rated as low, having been downgraded once for imprecision due to wide confidence intervals (SAEs were rare) and once for indirectness (single study with one type of LAMA and relatively short treatment duration).

Secondary outcomes

Exacerbations requiring hospitalisation

The confidence intervals were too wide to determine if there was a difference in the number of people who experienced an exacerbation requiring hospitalisation whilst taking a LAMA add-on versus an increased dose of ICS (OR 1.00, 95% CI 0.06 to 16.24; Analysis 1.4). The quality of the evidence was rated as low, having been downgraded once for imprecision due to wide confidence intervals (exacerbations were rare events), and once for indirectness (results may not be representative of LAMA as a class of drugs, and the treatment duration in the single included study was relatively short).

Fewer people taking a LAMA add-on had an exacerbation requiring admission to the emergency department compared with people taking double dose ICS (OR 0.49, 0.09 to 2.77; Analysis 1.5). The confidence intervals for this comparison excluded a significant effect: for people taking LAMA, we estimated that 12 fewer people per 1000 would have an exacerbation requiring admission to the emergency department, but the confidence intervals ranged from 21 fewer to 37 more people per 1000. The quality of the evidence was rated as low for the reasons described in the previous paragraph.

Lung function

Forced expiratory volume in one second (FEV_1)

We pre-specified this outcome as being our primary measure of lung function. The mean change from baseline in trough FEV_1 (L) was greater in people taking a LAMA-add on compared with those taking an increased dose of ICS (MD 0.10, 95% CI 0.03 to 0.17; Analysis 1.6).The evidence was rated as of moderate quality after being downgraded once for indirectness because the results may not be representative of LAMA as a class of drugs. The post-albuterol measurement also showed a smaller benefit of LAMA add-on compared with increasing ICS dose (MD 0.04, 95% CI 0.01 to 0.07; Analysis 1.7).

Peak expiratory flow (PEF)

The mean change from baseline in morning PEF (L/min) was greater in people taking a LAMA-add on compared with those taking an increased dose of ICS (MD in change from baseline 25.80, 95% CI 14.40 to 37.20; Analysis 1.8). Similarly, the mean change from baseline in evening PEF was greater in people taking a LAMA add-on (MD 35.30, 95% CI 24.60 to 46.00; Analysis 1.9).

Asthma control

Asthma control was found to be slightly improved in people taking a LAMA add-on compared with those taking an increased dose of ICS (MD in change from baseline − 0.18, 95% CI − 0.34 to − 0.02; Analysis 1.10). However, the magnitude of the mean difference between treatment groups (and confidence intervals) was below the established minimal clinically important difference (MCID) of 0.5 for the ACQ. The evidence was rated as low quality after being downgraded once for indirectness (evidence may not be representative of LAMA class) and once due to a risk of bias associated with the study design (see AQLQ above).

Adverse events

The published article (Peters 2010) reports that people taking the double dose of ICS had a higher number of unscheduled visits for asthma symptoms and events for which urgent care was needed compared with people taking a LAMA. We did not obtain additional data specifically for this endpoint. However, data relating to exacerbations and serious adverse events are provided above.

DISCUSSION

Summary of main results

One cross-over trial met the inclusion criteria for this review. The trial was performed in 210 patients with moderate to severe asthma and compared the use of beclomethasone 80 mcg twice daily plus tiotropium bromide 18 mcg once daily (morning) with double dose (160 mcg) beclomethasone twice daily (Peters 2010). The study was of good methodological quality and considered to be at low risk of bias for all domains except one.

Fewer people taking a LAMA add-on had an exacerbation requiring treatment with oral steroids compared with people taking double dose ICS, but the confidence intervals did not exclude the possibility that increased ICS dose was better: our results suggest that 18 fewer people per 1000 taking a LAMA would have an exacerbation requiring a course of OCS, but the confidence intervals ranged from 52 fewer to 26 more per 1000. Approximately equal numbers of people taking each treatment had an exacerbation requiring hospitalisation, but confidence intervals were too wide to suggest equivalence. Fewer people taking a LAMA had an exacerbation resulting in admission to an emergency department, but again the confidence intervals did not exclude benefit of an ICS dose increase. Being based on only a small number of events in

a single study, the quality of evidence for all of the exacerbation-related outcomes was rated as low. We downgraded the evidence based on imprecision and indirectness. Serious adverse events (all causes) also occurred in similarly low numbers of people taking each treatment, but the confidence intervals were too wide to conclude equivalence. Again, the evidence was downgraded to low quality due to imprecision and indirectness.

We did not find a significant difference in asthma-related quality of life between treatment groups. People taking a LAMA-add on scored slightly better on a scale measuring asthma control (ACQ) compared with people taking an increased dose of ICS. The magnitude of this effect was too small to be considered clinically significant, and the evidence for both of these measures (quality of life and asthma control) was considered as low quality, having been downgraded once for imprecision and once for risk of bias.

There was some evidence to support benefits of a LAMA add-on on lung function over an increased dose of ICS (as assessed by trough FEV_1, our prespecified measure for lung function). The quality of evidence for trough FEV_1 was rated as moderate, having been downgraded once for indirectness. Other measures of lung function (post-bronchodilator FEV_1, morning PEF and evening PEF) also showed a benefit of LAMA add-on. The quality of evidence for these other measures was not assessed, as they were not pre-specified as outcomes of interest in the review protocol.

Overall completeness and applicability of evidence

The current evidence base to address our research question is insufficient in several respects. Only one study was identified that met the inclusion criteria for this review, and no sub-group analyses were performed. The single included study used tiotropium delivered by Handihaler, so we cannot determine if our findings are applicable to other LAMA drugs such as glycopyrronium or aclidinium. Likewise, as the included study compared LAMA with an increased dose of beclomethasone, we cannot determine if the findings are relevant to other ICS. Several other studies of LAMA add-on have been completed or published (NCT01172808; Rajanandh 2014a), but double-dose ICS was not included as a comparison group, meaning that these studies are not fully representative of the guideline-recommended treatment options available to clinicians (BTS 2014; GINA 2014).

The included study (Peters 2010) used a cross-over design in which 210 participants were randomly assigned to the order in which they received three treatments, each for 14 weeks (only two treatment periods were relevant to this review). The duration of the washout periods between treatment regimens was relatively short (14 days). Studies in patients with asthma have shown that ICS can have prolonged effects (Haahtela 1994; Juniper 1991) for up to several weeks after treatment cessation (De Blic 1996). Thus, in the cross-over study reported by Peters and colleagues, carryover effects could have confounded the results from the tiotropium treatment period if patients were randomised to receive the higher dose of ICS first. Indeed, a degree of carryover effect appeared to affect the results relating to the number of asthma control days and could have had an impact on the magnitude of difference for the other outcomes we assessed. The duration of treatment in the included study was also relatively short. Therefore, we would urge a cautious interpretation of our findings in the context of the medium- to long-term use of LAMA plus ICS, particularly in terms of safety.

The use of LAMA for asthma is relatively new, with only one UK licence extension for Spiriva Respimat to be used in combination with LABA plus ICS for patients with asthma. We anticipate that the evidence base for this topic will grow as more products are approved for this indication. Thus, we hope that the applicability of findings from future versions of this review will broaden.

Quality of the evidence

The quality of the evidence relating to two of our primary outcomes, exacerbations and serious adverse events, was rated as low. This was because only one study was included in this review and therefore the evidence is based on findings for only one member of the LAMA class (tiotropium) and may not be representative of the class as a whole. Additionally, the duration of each treatment period in the included study was only 14 weeks, so the evidence relating to exacerbations and serious adverse events (i.e. relatively rare events) cannot be considered representative of the long-term use of these drugs.

The quality of evidence for quality of life and asthma control was also considered to be low, having been downgraded for indirectness and also risk of bias due to evidence of a carryover effect between treatment periods in the included study, which used a cross-over design.

The evidence for lung function (using trough FEV_1) was graded as moderate. This decision was based on a single downgrade for indirectness as discussed above. Notably, the data were extracted from a cross-over trial where each participant acted as their own control, hence increasing the power of the study relative to a study of parallel design and similar size. Although we pre-specified FEV_1 as the primary measure of lung function, other measures of lung function (PEF and post-bronchodilator FEV_1) were not pre-specified and consequently not assessed for quality of evidence. The lack of well-established, minimally important differences for lung function measures made it difficult to interpret the clinical significance of the magnitude and precision of the difference between LAMA add-on and increased dose ICS. A change of approximately 10% from baseline in FEV_1 was reported as the MCID for asthma patients, although this was based on patient perception of change and is not well established (Reddel 2009). Using this threshold in relation to the participants' baseline pre-albuterol FEV_1, 100 mL would not be considered clinically important, but changes in

morning and evening PEF were above a reported MCID of 18.8L/min (Reddel 2009).

Potential biases in the review process

The review was conducted to the standards set by MECIR 2013 and in accordance with the published protocol (Kew 2014). There were several deviations from the protocol (see Differences between protocol and review), the majority of which arose due to the inclusion of a single study in the review.

It is unlikely that any relevant studies were missed, as a skilled information specialist conducted the main electronic searches. Additionally, the main searches were supplemented by extensive searches of several 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, WHO trials portal). We also contacted the authors of the included study, who provided all requested additional or missing data and study information that was not available in the published report.

Agreements and disagreements with other studies or reviews

Several other systematic reviews have considered the use of LAMA for asthma (Befakadu 2014; Rashid 2014; Rodrigo 2015) but only Befakadu compared the LAMA versus increased dose of ICS (without LABA). Their narrative synthesis for the LAMA versus double-ICS comparison was also based on the single study by Peters 2010. The authors noted that tiotropium was superior to doubling the dose of ICS, but this was based on the primary outcome of the study, morning peak expiratory flow, which we did not consider as the primary measure of lung function in this review. Befakadu and colleagues also noted evidence of improved lung function in patients taking LAMA plus ICS compared with those taking increased doses of ICS; the authors concluded that it remains to be seen whether the lung function improvements will result in long-term symptom improvement. These findings are generally in line with those of this review.

AUTHORS' CONCLUSIONS

Implications for practice

Only one randomised trial was found, comparing tiotropium add-on to increased dose beclomethasone. Differences between the treatments were generally too small or imprecise to tell whether adding a LAMA to ICS is safer or more effective than increasing the dose of ICS, and there is a possibility of carryover effects due to the study's cross-over design. LAMA add-on may lead to more improvement in lung function (FEV_1) than increasing ICS dose.

Implications for research

The results of this review, alongside pending results from related reviews assessing the use of LAMA against other treatments, will help to define the role of these drugs in asthma and should be updated as results from future trials emerge. Studies assessing the role of LAMA add-on should be longer and include a double-ICS treatment arm so that the results can be interpreted in the context of the guideline-recommended treatment options that are available to physicians.

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REFERENCES

References to studies included in this review

Peters 2010 *{published and unpublished data}*

Lane M. Tiotropium bromide in asthma patients: an alternative to inhaled long-acting beta-agonists?. *Journal of the Royal College of Physicians of Edinburgh* 2010;**40**(4): 321–2.

NCT00565266. Asthma Clinical Research Network (ACRN) Trial - Tiotropium bromide as an alternative to increased inhaled corticosteroid in patients inadequately controlled on a lower dose of inhaled corticosteroid (TALC). http://clinicaltrials.gov/show/NCT00565266 (accessed 19 January 2015).

Peters SP, Bleecker ER, Kunselman SJ, Icitovic N, Moore WC, Pascual R, et al. Predictors of response to tiotropium versus salmeterol in asthmatic adults. *The Journal of Allergy and Clinical Immunology* 2013;**132**(5):1068–74.

* Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *New England Journal of Medicine* 2010;**363**(18):1715–26.

References to studies excluded from this review

Beeh 2013 *{published data only}*

Beeh KM, Ablinger O, Moroni-Zentgraf P, Hollaenderova Z, Pivovarova A, Engel M, et al. Once-daily add-on tiotropium: A dose-finding trial in adult patients with moderate persistent asthma [Abstract]. *Allergy* 2013;**68** (s97):376–7.

Bernstein 2013 *{published data only}*

Bernstein JA, Kerstjens HAM, Moroni-Zentgraf P, Engel M, Schmidt H, Halpin DMG. Once-daily tiotropium is well tolerated as add-on to standard treatment for patients with symptomatic asthma despite receiving inhaled corticosteroids and long-acting beta$_2$-agonists [Abstract]. *Chest* 2013;**144**(4 Meeting Abstracts):89A.

Casale 2014 *{published data only}*

Casale TB, Bateman ED, Dahl R, Pizzichini E, Vandewalker ML, Virchow JC, et al. Tiotropium Respimat add-on therapy reduces airflow obstruction in patients with symptomatic moderate asthma, independent of T_H2 inflammatory status [Abstract]. *The Journal of Allergy and Clinical Immunology* 2014;**133**(2 Suppl):AB5.

Casale TB, Bleecker ER, Meltzer E, Pizzichini E, Schmidt O, Bateman ED, et al. Phase III trials to investigate tiotropium as add-on therapy to inhaled corticosteroids for patients with symptomatic asthma: trial design and planned statistical analyses [Abstract]. *Allergy* 2013;**68**(Suppl 97): 377.

Corren 2014 *{published data only}*

Corren J, Murphy KR, Bensch G, Dahl R, Paggiaro P, Engel M, et al. Once-daily tiotropium respimat decreases the risk of exacerbations, independent of baseline characteristics, in patients with symptomatic severe asthma without evidence of chronic obstructive pulmonary disease. *Journal of General Internal Medicine* 2014;**29**:S157–8.

CTRI/2008/091/000306 *{published data only}*

CTRI/2008/091/000306. A randomized, double-blind, crossover, non-inferiority study comparing bronchodilator effects of single dose of 18 mcg of Tiotropium Bromide and two doses of 12 mcg of formoterol fumarate each over 24 hours in subjects with moderate to severe asthma. http://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=284&EncHid=&modid=&compid=%27,%27284det%27 (accessed 19 January 2015).

CTRI/2012/08/002915 *{published data only}*

CTRI/2012/08/002915. Assessment of various second line treatment regimens on mild to moderate persistent asthmatic patients. http://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=5059&EncHid=&modid=&compid=%27,%275059det%27 (accessed 19 January 2015).

Dahl 2014a *{published data only}*

Dahl R, Doherty DE, Corren J, Karpel J, Kerstjens HAM, Engel M, et al. Once-daily tiotropium respimat improves lung function in patients with severe symptomatic asthma independent of leukotriene modifier use [Abstract]. *The Journal of Allergy and Clinical Immunology* 2014;**133**(2 Suppl):AB5.

Dahl 2014b *{published data only}*

Dahl R, Bateman ED, Casale TB, Pizzichini E, Vandewalker M, Virchow JC, et al. Once-daily tiotropium Respimat as add-on to at least medium- to high-dose ICS, with or without LABA, improves lung function in patients with symptomatic asthma, independent of allergic status [Abstract]. 33rd Congress of the European Academy of Allergy and Clinical Immunology; 2014 June 7-11; Copenhagen. 2014.

Doherty 2013 *{published data only}*

Doherty DE, Tashkin DP, Harrison TW, Engel M, Schmidt H, Moroni-Zentgraf P, et al. Improvements in lung function with tiotropium as add-on controller therapy to ICS+LABA for patients with symptomatic severe asthma [Abstract]. *Chest* 2013;**144**(4 Meeting Abstracts):88A.

EUCTR2006-003385-34-NL *{published data only}*

EUCTR2006-003385-34-NL. The effect of tiotropium-bromide on deep inspiration-induced bronchodilation and airway responsiveness in asthma. https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-003385-34/NL/#A (accessed 19 January 2015).

Haggart 2004 *{published data only}*

Haggart K, Fardon TC, Lee DKC, Lipworth BJ. Stepping down inhaled steroids in severe asthma with long acting bronchodilators: utilising effort dependent and independent measures of pulmonary function [Abstract]. *Thorax* 2004; **59**(Suppl 2):ii72.

Halpin 2010 *{published data only}*

Halpin DMG, Bateman ED, Tashkin DP, Engel M, Dahl R, Paggiaro P, et al. Tiotropium decreases the risk of exacerbations in patients with symptomatic asthma regardless of baseline characteristics including markers of allergic status [Abstract]. *Thorax* 2013;**68**(Suppl 3):A149.

Howaza 2013 *{published data only}*

Hozawa S, Kerstjens HAM, Tashkin DP, Engel M, Ronald D, Paggiaro P, et al. Tiotropium decreases the risk of exacerbations in patients with symptomatic asthma regardless of baseline characteristics [Abstract]. *Respirology* 2013;**18**(S4):175.

JPRN-UMIN000010352 *{published data only}*

JPRN-UMIN000010352. Study for effects of tiotropium on smokers and non-smokers with bronchial asthma. http://www.umin.ac.jp/ctr/index.htm (accessed 19 January 2015).

Kerstjens 2012 *{published data only}*

Corren J, Frew A, Engel M, Schmidt H, Moroni-Zentgraf P, Kerstjens HAM. Tiotropium as add-on therapy to ICS+LABA in patients with symptomatic severe asthma: spirometric assessment over 24 hours [Abstract]. *Chest* 2013;**144**(4 Meeting Abstracts):91A.

Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *New England Journal of Medicine* 2012;**367**(13):1198–207.

Vandewalker ML, Engel M, Schmidt H, Siebold W, Moroni-Zentgraf P, Kerstjens HAM, et al. Efficacy of tiotropium in patients with asthma in relation to allergic status [Abstract]. *The Journal of Allergy and Clinical Immunology* 2013;**131**(2 Suppl 1):AB1.

NCT00350207 *{published data only}*

Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *The Journal of Allergy and Clinical Immunology* 2011;**128**(2):315–22.

NCT00350207. A 16-week randomised, placebo-controlled, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of tiotropium inhalation solution delivered by the Respimat inhaler (2 actuations of 2.5 mcg once daily) with that of salmeterol from the hydrofluoroalkane metered dose inhaler (2 actuations of 25 mcg twice daily) in moderate persistent asthma patients with the B16-Arg/Arg genotype. http://clinicaltrials.gov/show/NCT00350207 (accessed 19 January 2015).

NCT00557180 *{published data only}*

NCT00557180. Obesity, Inflammation and Response to Therapy in Asthma - Ancillary to Asthma Clinical Research Network (ACRN) Trials. https://clinicaltrials.gov/ct2/show/NCT00557180 (accessed 19 January 2015).

NCT00706446 *{published data only}*

NCT00706446. Genotype stratified treatment with anticholinergic vs. beta-agonist (long acting) and exacerbations (GABLE). http://clinicaltrials.gov/show/NCT00706446 (accessed 19 January 2015).

NCT01172808 *{published data only}*

NCT01172808. A phase III randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 and 5 µg once daily) compared with placebo and salmeterol HFA MDI (50 µg twice daily) over 24 weeks in moderate persistent asthma. http://clinicaltrials.gov/show/NCT01172808 (accessed 19 January 2015).

NCT01172821 *{published data only}*

NCT01172821. A Phase III randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 and 5 µg once daily) compared with placebo and salmeterol HFA MDI (50 µg Twice Daily) over 24 weeks in moderate persistent asthma. http://clinicaltrials.gov/show/NCT01172821 (accessed 19 January 2015).

NCT01290874 *{published data only}*

NCT01290874. Blacks and Exacerbations on LABA vs. Tiotropium (BELT). http://clinicaltrials.gov/show/NCT01290874 (accessed 19 January 2015).

NCT01316380 *{published data only}*

NCT01316380. A Phase III, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 ug and 5 ug once daily) compared to placebo over 12 weeks in mild persistent asthma. http://clinicaltrials.gov/show/NCT01316380 (accessed 19 January 2015).

NCT01340209 *{published data only}*

NCT01340209. A Phase III randomised, double-blind, placebo-controlled, parallel-group trial to evaluate safety and efficacy of tiotropium inhalation solution delivered via Respimat inhaler (2.5 and 5 µg Once Daily) compared with placebo over 52 weeks in patients with moderate to severe persistent asthma. http://clinicaltrials.gov/show/NCT01340209 (accessed 19 January 2015).

NCT01573624 *{published data only}*

NCT01573624. A multi-center, randomized, double-blind, dose-ranging study to evaluate GSK573719 in combination with fluticasone furoate, fluticasone furoate alone, and an active control of fluticasone furoate/vilanterol combination in subjects with asthma. http://clinicaltrials.gov/show/NCT01573624 (accessed 19 January 2015).

NCT01641692 *{published data only}*

NCT01641692. A multi-national, randomized, double-blind, placebo-controlled, 3-period crossover study with GSK 573719 as monotherapy in adult subjects with asthma. http://clinicaltrials.gov/show/NCT01641692 (accessed 19 January 2015).

NCT01696214 ***{published data only}***

NCT01696214. SAPS: smoking asthmatics pilot study. http://clinicaltrials.gov/show/NCT01696214 (accessed 19 January 2015).

NCT02127697 ***{published data only}***

NCT02127697. A randomized, double-blind, parallel group, 52-week study evaluating the efficacy, safety and tolerability of NVA237 in patients with poorly controlled asthma. http://clinicaltrials.gov/show/NCT02127697 (accessed 19 January 2015).

Paggiaro 2013 ***{published data only}***

Paggiaro P, Engel M, Tudoric N, Forstner B, Radeczky E, Zubek V, et al. Phase III trial of tiotropium as add-on therapy to low-dose inhaled corticosteroids for patients with symptomatic mild persistent asthma: Design and planned analyses [Abstract]. *European Respiratory Journal* 2013;**42** (Suppl 57):877s [P4133].

Paggiaro 2014 ***{published data only}***

Paggiaro P, Halpin DMG, Buhl R, Engel M, Zubek V, Blahova Z, et al. Tiotropium respimat add-on to inhaled corticosteroids improves lung function in patients with symptomatic mild asthma: Results from a phase III trial. *The Journal of Allergy and Clinical Immunology* 2014;**133**(2 Suppl):AB4.

Rajanandh 2014a ***{published data only}***

Rajanandh MG, Nageswari AD, Ilango K. Assessment of various second-line medications in addition to inhaled corticosteroid in asthma patients: a randomized controlled trial. *Clinical and Experimental Pharmacology and Physiology* 2014;**41**(7):509–13.

Rajanandh 2014b ***{published data only}***

Rajanandh MG, Nageswari AD, Ilango K. Pulmonary function assessment in mild to moderate persistent asthma patients receiving montelukast, doxofylline, and tiotropium with budesonide: a randomized controlled study. *Clinical Therapeutics* 2014;**36**(4):526–33.

Tashkin 2013 ***{published data only}***

Tashkin DP, Moroni-Zentgraf P, Engel M, Schmidt H, Kerstjens HAM. Once-daily tiotropium reduces risk of exacerbations and asthma worsening in patients with symptomatic asthma despite treatment with inhaled corticosteroids and long-acting beta2-agonists [Abstract]. *Chest* 2013;**144**(4 Meeting Abstracts):90A.

Vogelberg 2014 ***{published data only}***

Vogelberg C, Engel M, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, Sigmund R, Downie J, et al. Once-daily tiotropium in adolescents with symptomatic asthma despite inhaled corticosteroid treatment: a dose-ranging study [Abstract]. *Clinical and Translational Allergy* 2014;**4** (Suppl 1):O5.

Additional references

Adams 2008a

Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Beclomethasone versus placebo for chronic asthma. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD002738.pub2]

Adams 2008b

Adams NP, Bestall JC, Lasserson TJ, Jones P, Cates CJ. Fluticasone versus placebo for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD003135.pub4]

Allison 2014

Allison DE, Kew KM, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS for adults with asthma. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD011397]

Anderson 2005

Anderson HR. Prevalence of asthma. *British Medical Journal* 2005;**330**:1037.

Bateman 2004

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *American Journal of Respiratory and Critical Care Medicine* 2004;**170**(8):836–44.

Befakadu 2014

Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. *Journal of Asthma and Allergy* 2014;**7**: 11–21.

BNF

Royal Pharmaceutical Society. British National Formulary (online). http://www.medicinescomplete.com. Royal Pharmaceutical Society, (accessed 27 August 2014).

Brozek 2008 [Computer program]

Brozek J, Oxman A, Schünemann H. GradePro Version 3.2 for Windows. Hamilton (Ontario): McMaster University, 2014, 2008.

BTS 2014

British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax* 2014;**69**(Suppl. 1):i1–i192.

Chauhan 2014

Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database of Systematic Reviews* 2014, Issue 1. [DOI: 10.1002/14651858.CD003137.pub5]

Chinchilli 2015 [pers comm]

Chinchilli VM. Allocation concealment used in our trial [personal communication]. Email to: D Evans. 16 January 2015.

Chong 2012

Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD009157.pub2]

Covidence [Computer program]
The Alfred Hospital, Monash University, National ICT Australia and the University of London. Covidence. Melbourne: Alfred Health, 2013.

De Blic 1996
De Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *The Journal of Allergy and Clinical Immunology* 1996;**98**(1): 14–20.

Ducharme 2008
Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2008, Issue 5. [DOI: 10.1002/14651858.CD005535.pub2]

Ducharme 2010
Ducharme FM, Ni Choinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD005533.pub2]

Elbourne 2002
Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

eMC 2014
Electronic Medicines Compendium (eMC). License extension 19th September 2014: Spiriva Respimat 2.5 micrograms solution for inhalation. https://www.medicines.org.uk/emc/history/20134 (accessed 24 October 2014).

GINA 2014
Global Initiative for Asthma. Global Strategy For Asthma Management And Prevention. http://www.ginasthma.org/documents/4 (accessed 22 August 2014).

Global Asthma Report 2014
International Union Against Tuberculosis and Lung Disease. The Global Asthma Report 2014. The Global Asthma Report 2014, http://www.globalasthmareport.org (accessed 28th August 2014).

Gosens 2006
Gosens R, Zaagsma J, Meurs H, Halayko AJ. Muscarinic receptor signaling in the pathophysiology of asthma and COPD. *Respiratory Research* 2006;**7**(1):73.

Haahtela 1994
Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide inpatients with mild asthma. *New England Journal of Medicine* 1994;**331**(11):700–5.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Juniper 1991
Juniper EF, Kline PA, Vanzieleghem MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. *The Journal of Allergy and Clinical Immunology* 1991;**87**(2):483–9.

Juniper 2006
Juniper EF, Bousquet J, Abetz L, Bateman ED, GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respiratory Medicine* 2006;**100**(4):616–21.

Karner 2014
Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2014, Issue 7. [DOI: 10.1002/14651858.CD009285.pub3]

Kew 2015
Kew KM, Evans DJW, Allison DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: 10.1002/14651858.CD011438.pub2]

Lipworth 2014
Lipworth BJ. Emerging role of long acting muscarinic antagonists for asthma. *British Journal of Clinical Pharmacology* 2014;**77**(1):55–62.

MECIR 2013
Chandler J, Churchill R, Higgins J, LassersonT, Tovey D. Methodological Expectations for the conduct of Cochrane Intervention Review, version 2.3. http://editorial-unit.cochrane.org/mecir. (accessed 3rd Feb 2015).

Moulton 2011
Moulton BC, Fryer AD. Muscarinic receptor antagonists, from folklore to pharmacology; finding drugs that actually work in asthma and COPD. *British Journal of Clinical Pharmacology* 2011;**163**(1):44–52.

Ni 2014
Ni H, Soe Z, Moe S. Aclidinium bromide for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2014, Issue 9. [DOI: 10.1002/14651858.CD010509.pub2]

NICE 2013
National Institute for Health and Care Excellence. NICE advice [KTT5] High-dose inhaled corticosteroids in asthma. http://www.nice.org.uk/Advice/ktt5 (accessed 29 August 2014).

NRAD 2014
Royal College of Physicians. *Why Asthma Still Kills: The National Review of Asthma Deaths (NRAD) Confidential Enquiry Report*. London: Royal College of Physicians, 2014.

Rashid 2014
Rashid Q, Klein R. Tiotropium in the treatment of patients with asthma. *Southern Medical Journal* 2014;**107**(5):330–7.

Reddel 2009
Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;**180**(1):59–99.

RevMan [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rodrigo 2015
Rodrigo GJ, Castro-Rodríguez JA. What is the role of tiotropium in asthma?: A systematic review with meta-analysis. *Chest* 2015;**147**(2):388–96.

Tee 2009
Tee A, Koh MS, Gibson PG, Lasserson TJ, Wilson A, Irving LB. Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD001281.pub2]

Verhamme 2013
Verhamme KM, Afonso A, Romio S, Stricker BC, Brusselle GG, Sturkenboom MC. Use of tiotropium Respimat Soft Mist Inhaler versus HandiHaler and mortality in patient with COPD. *European Respiratory Journal* 2013;**42**(3):606–15.

Wise 2013
Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, et al. Tiotropium Respimat Inhaler and the risk of death in COPD. *New England Journal of Medicine* 2013;**369**(16):1491–501.

References to other published versions of this review

Kew 2014
Kew KM, Allison DE, Evans DJW, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma. *Cochrane Database of Systematic Reviews* 2014, Issue 12. [DOI: 10.1002/14651858.CD011437]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Peters 2010

Methods	**Study design:** RCT **Study grouping:** cross-over **Open Label:** NO **Cluster RCT:** NO
Participants	**Baseline Characteristics:** For the whole population, patients received the treatments in a random sequence with washout • Setting: 10 university medical centres; outpatient services. • Country: USA. • Mean age in years (SD): 42.2 (±12.3) • % male: 32.9 • % white: 54.8 • FEV_1 (% predicted (SD)): 71.5 (±14.9) • Duration of asthma in years (SD): 26.1 (±14.1) • Number randomised: 210 • Number completed: 174 **Inclusion criteria:** at least 18 years of age; clinical history consistent with asthma; FEV_1 > 40% predicted value; asthma confirmed by beta-agonist reversibility to four puffs albuterol of ≥ 12%; OR methacholine provocative concentration at 20% (PC_{20}) of ≤ 8 mg/mL (not on ICS), or ≥ 16 mg/mL (on ICS); need for daily controller therapy (i.e. ICS, leukotriene modifiers, long-acting beta-agonists, or a combination of these); received prescription for or used asthma controller in previous 12 months; OR symptoms > twice a week and not on asthma controller; if on ICS, stable dose for at least two weeks not exceeding 1000 mcg fluticasone or equivalent daily; non-smoker for at least one year and total lifetime history < 10 pack-years; if female of child-bearing potential, willing to use an effective form of birth control throughout the study; able to measure morning PEF on schedule using meter and to complete the study diary correctly at least 75% of the time during week 2 to 4 run-in interval; ≥ 75% adherence with study medication during run-in; no asthma exacerbation requiring oral corticosteroids or additional asthma medications (including an increased dose of ICS) during the run-in **Exclusion criteria:** Lung disease or additional medical diagnosis other than asthma, including COPD and chronic bronchitis; established or suspected diagnosis of vocal cord dysfunction; respiratory tract infection or significant asthma exacerbation in previous four weeks; history of life-threatening asthma requiring treatment with intubation and mechanical ventilation in previous five years; hyposensitisation therapy other than an established maintenance regimen; inability to coordinate use of the delivery devices used in the study; pregnant
Interventions	**Intervention Characteristics** ICS + LAMA add-on • ICS type and dose: beclomethasone dipropionate, 80 mcg twice daily • LAMA type and dose: tiotropium bromide inhalation powder, 18 mcg once daily • Inhaler type: tiotropium, SPIRIVA HandiHaler; beclomethasone, QVAR Inhalation Aerosol

	• Background medications: all other asthma medications stopped • Duration of treatment: 14-week treatment period followed by 2-week washout ICS dose increase • ICS type and dose: beclomethasone dipropionate, 160 mcg twice daily • LAMA type and dose: NA • Inhaler type: beclomethasone, QVAR Inhalation Aerosol • Background medications: all other asthma medications stopped • Duration of treatment: 14-week treatment period followed by 2-week washout
Outcomes	*Continuous*: • Morning PEF L/min • Evening PEF L/min • Trough FEV_1 (L) • ACQ • AQLQ • Quality of life • Asthma control • Lung function *Dichotomous*: • Exacerbations (OCS) • SAEs (all) • Exacerbations (ED) • AEs (all) • Exacerbations (hospital)
Identification	**Sponsorship source**: National Heart, Lung, and Blood Institute **Author name**: Vernon M Chinchilli, PhD **Institution:** Penn State Hershey College of Medicine **Email:** vchinchi@psu.edu **Tel:** +1 717-531-4262
Notes	**Baseline characteristics:** % predicted FEV_1 was taken at visit 3 before bronchodilation, the baseline for the first treatment period **Continuous outcomes:** Continuous outcomes were extracted as contrasts to be entered in GIV as this is most appropriate for cross-over trials **Dichotomous outcomes:** Most patients who had an exacerbation requiring OCS were also treated with intravenous steroids; one patient received intravenous steroids only and was considered a 'yes' for this outcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Communication with trial authors: "The Data Coordinating Centre (DCC) generated the randomisation scheme via the sta-

		tistical software package SAS."
Allocation concealment (selection bias)	Low risk	Communication with trial authors: "The network pharmacist constructed the blinded drug packets according to the randomisation scheme, and then the drug packets were shipped to the clinical centres. The DCC developed a web-based system in which the study coordinator at a clinical centre logged into the website whenever an eligible patient was ready for randomisation, entered the appropriate information into the randomisation module, and then was notified by the randomisation module as to the appropriate drug packet for that eligible patient."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Participants and personnel were blinded to knowledge of which intervention participants received. The clinical trial register (clinicaltrial.gov) states, "Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)." The primary manuscript states, "In a three-way, double-blind, triple-dummy cross-over trial . . ." and the methods specify that placebo inhalers were used [for blinding purposes]
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Blinding on ClinicalTrials.gov described as subject, caregiver, investigator, outcomes assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Less than 10% of patients in each group withdrew from the study. Although more patients in the double ICS group dropped out (8%) than in the LAMA add-on group (4%), the numbers of patients dropping out due to adverse events was similar between groups. The difference arose due to 10 patients withdrawing consent in the double ICS group compared with only 3 in the LAMA add-on group. We were provided with the ITT[q] dataset, however comparison with the dataset based on patients who had an event or completed follow-up showed little or no difference in the overall results

Selective reporting (reporting bias)	Low risk	Comment: The primary outcome and the majority of secondary outcomes (i.e. as specified in the protocol and ClinicalTrials.gov record) are reported for the research hypothesis of interest. The secondary biomarker outcomes were not reported, other than to state that "levels of inflammatory biomarkers were low at baseline and thereafter". However, lack of the biomarker data in the primary paper do not influence assessment of safety or efficacy. There is a high risk of bias for the outcome 'asthma exacerbations' as the authors did not pre-specify the presentation of this outcome, instead choosing 'number of patients with an exacerbation' (rather than time to first exacerbation or total number of exacerbations in a treatment group adjusted for total follow-up for the given intervention)
Other bias	High risk	HIGH: Quotation: "Although minimal carryover effects between periods were observed for measures of lung function, an effect was seen for asthma control days." LOW: Quotation: "The company had no role in the performance of the trial, the analysis or interpretation of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication."

ACQ: Asthma Control Questionnaire; AE: adverse events; AQLQ: Asthma Quality of Life Questionnaire; COPD: chronic obstructive pulmonary disease; ED: emergency department; FEV_1: forced expiratory volume in one second; GIV: generic inverse variance; ICS: inhaled corticosteroids; ITT: intention to treat; LAMA: long-acting muscarinic antagonist; NA: not applicable; OCS: oral corticosteroids; PC_{20}: histamine provocative concentration causing a 20% drop in FEV_1; PEF: peak expiratory flow; RCT: randomised controlled trial; SAEs: serious adverse events; SD: standard deviation.

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

Study	Reason for exclusion
Beeh 2013	Duration of study too short
Bernstein 2013	Greater than 50% of participants taking LABA

(*Continued*)

Casale 2014	Wrong comparator
Corren 2014	Greater than 50% of participants taking LABA
CTRI/2008/091/000306	Wrong comparator
CTRI/2012/08/002915	Wrong comparator
Dahl 2014a	Greater than 50% of participants taking LABA
Dahl 2014b	Greater than 50% of participants taking LABA
Doherty 2013	Greater than 50% of participants taking LABA
EUCTR2006-003385-34-NL	Wrong comparator
Haggart 2004	Wrong intervention
Halpin 2010	Greater than 50% of participants taking LABA
Howaza 2013	Greater than 50% of participants taking LABA
JPRN-UMIN000010352	Wrong comparator
Kerstjens 2012	Greater than 50% of participants taking LABA
NCT00350207	Wrong comparator
NCT00557180	Observational cohort study
NCT00706446	Wrong comparator
NCT01172808	Wrong comparator
NCT01172821	Wrong comparator
NCT01290874	Wrong comparator
NCT01316380	Wrong comparator
NCT01340209	Wrong comparator
NCT01573624	Wrong comparator
NCT01641692	Duration of study too short

(*Continued*)

NCT01696214	Wrong comparator
NCT02127697	Wrong comparator
Paggiaro 2013	Wrong comparator
Paggiaro 2014	Wrong comparator
Rajanandh 2014a	Wrong comparator
Rajanandh 2014b	Wrong comparator
Tashkin 2013	Greater than 50% of participants taking LABA
Vogelberg 2014	Duration of study too short

DATA AND ANALYSES

Comparison 1. ICS + LAMA add-on *vs.* ICS dose increase

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring a course of OCS	1		Odds Ratio (Random, 95% CI)	Totals not selected
2 Asthma QoL questionnaire score	1		Mean Difference (Random, 95% CI)	Totals not selected
3 SAEs (all cause)	1		Odds Ratio (Random, 95% CI)	Totals not selected
4 Exacerbations (hospital)	1		Odds Ratio (Random, 95% CI)	Totals not selected
5 Exacerbations (ED)	1		Odds Ratio (Random, 95% CI)	Totals not selected
6 FEV1 pre-albuterol (L)	1		Mean Difference (Random, 95% CI)	Totals not selected
7 FEV1 post-albuterol (L)	1		Mean Difference (Random, 95% CI)	Totals not selected
8 Morning PEF (L/min)	1		Mean Difference (Random, 95% CI)	Totals not selected
9 Evening PEF (L/min)	1		Mean Difference (Random, 95% CI)	Totals not selected
10 Asthma Control Questionnaire score	1		Mean Difference (Random, 95% CI)	Totals not selected

CONTRIBUTIONS OF AUTHORS

Kayleigh Kew wrote the background and methods, with comments and editing from Debbie Allison and Anne Boyter. All authors also contributed to the design and writing of two related reviews, which were produced in parallel and informed the writing of this review. David Evans constructed the analyses and wrote the results and discussion with support from Kayleigh and comments from Debbie and Anne. All authors approved the final version of the document.

DECLARATIONS OF INTEREST

Kayleigh Kew: none known

Debbie Allison: none known

Anne Boyter: none known

David Evans: none known

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Internal sources

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External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As there was only one included study, no meta-analyses, sensitivity analyses or subgroup analyses could be performed.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage]; Anti-Asthmatic Agents [administration & dosage]; Asthma [*drug therapy]; Beclomethasone [administration & dosage]; Cross-Over Studies; Muscarinic Antagonists [*administration & dosage]; Randomized Controlled Trials as Topic; Tiotropium Bromide [administration & dosage]

MeSH check words

Adult; Humans