Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma (Protocol)

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[Intervention Protocol]

Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of adding a long-acting muscarinic agonist (LAMA) to inhaled corticosteroids (ICS) compared with adding a long-acting beta$_2$-agonist (LABA) for adults whose asthma is not well controlled on ICS alone.

BACKGROUND

Description of the condition

Asthma is a 'common and potentially serious chronic disease' of the airways, which 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 commonly causes symptoms including '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 2011), and 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 World Health Organisation estimates suggest 300 million people are affected worldwide, with direct treatment costs and indirect costs of lost productivity among the highest for non-communicable diseases (Global Asthma Report 2011). 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 the severity and frequency of symptoms according to treatment 'steps' laid out in guidelines (e.g. GINA 2014).

Depending on symptom control and frequency of exacerbations when treatment has been commenced, therapy can be 'stepped up' by increasing dose or adding medications to recapture control, or 'stepped down' to maintain patients at the lowest effective therapy and minimise side-effects.

Description of the intervention

The lowest treatment step in most guidelines is the sole use of a short-acting bronchodilating inhaler on an as-needed basis (e.g. salbutamol), which is often sufficient to treat mild or intermittent asthma symptoms. Regular use of low dose inhaled corticosteroids (ICS) is the primary recommended preventer therapy for people with persistent asthma who remain inadequately controlled on as-needed medication alone (Step 2, GINA 2014). Regular ICS has been shown to improve lung function and reduce the need for reliever medications (Adams 2008; Adams 2008a). However, some people with asthma will continue to have symptoms and asthma attacks on ICS alone and guidelines suggest a range of treatment options for this group of patients (step 3 and above). Long-acting beta-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). Despite these proven benefits, LABA have been linked to increased morbidity and mortality in asthma (Nelson 2006; Salpeter 2006; Cates 2014), leading to an FDA black box warning to highlight the increased risk of serious adverse events (FDA 2010). While the risks are reduced when LABA are used as an add-on treatment to ICS (Ernst 2006; Cates 2014), it is still unclear whether the risk of adverse events remains higher than with ICS alone (Ducharme 2008).

Inhaled corticosteroids also carry risks and add-on drugs that allow their dose to be kept low are often seen as preferable to high dose monotherapy. 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 COPD (Karner 2014) are now being considered as an alternative to LABA add-on therapy for adults with asthma requiring more than ICS alone. Tiotropium, the first LAMA to be licensed in COPD and the most widely used, has demonstrated added benefits over LABA in terms of 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 emerging but less well established (Ni 2014).

How the intervention might work

Long-acting muscarinic antagonists 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 and the overlap in pathophysiology and symptoms of asthma and COPD (Gosens 2006) have led to their testing in asthma as an add-on therapy for patients who do not achieve adequate control from standard-dose ICS alone, thus 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 or diarrhoea, cough, and headache (BNF). All LAMA for maintenance treatment of airways disease are delivered via inhalers, either by powder (HandiHaler, Genuair, Breezhaler) or soft mist delivery (Respimat), and are not suitable for use 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 increases the risk of death, particularly cardiac, compared with placebo and the same drug 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

Only one preparation of LAMA (Spiriva Respimat 2.5 mcg) has been granted a UK license for use in severe asthma alongside LABA and ICS (eMC 2014). Following its demonstrated efficacy in COPD (Karner 2014), clinical trials are emerging testing various LAMA regimens against the existing treatment options. One study found that nearly 30 per cent of patients who were uncontrolled on fluticasone remained so with the guideline recommended addition of LABA (Bateman 2004), suggesting there is a need for additional therapeutic options. It is therefore important to assess the efficacy and safety of LAMA add-on against LABA add-on, since the latter is the preferred step-up treatment when ICS alone are ineffective (GINA 2014).

Three other reviews are currently being produced to assess 1) LAMA add-on compared with increasing ICS dose 2) LAMA add-on and compared with no change to ICS dose, and 3) LAMA add-on as triple therapy with LABA+ICS compared with LABA+ICS alone.

OBJECTIVES

To assess the efficacy and safety of adding a long-acting muscarinic agonist (LAMA) to inhaled corticosteroids (ICS) compared with adding a long-acting beta$_2$-agonist (LABA) for adults whose asthma is not well controlled on ICS alone.

METHODS

Criteria for considering studies for this review

Types of studies

We will include double-blinded parallel or crossover randomised controlled trials (RCTs) of at least 12 weeks' duration. We will include studies reported as full-text, those published as abstract only, and unpublished data.
We will not exclude studies on the basis of blinding.

Types of participants

We will include adults (18+) whose asthma is not well controlled on ICS alone. We will exclude trials that include participants with other chronic respiratory co-morbidities (e.g. chronic obstructive pulmonary disease, bronchiectasis).
If studies include adults and adolescents or children under 12 and data are not reported separately, we will include them if the mean age in both groups is over 18.

Types of interventions

We will include trials comparing the addition of a LAMA add-on with LABA add-on. Any dose of ICS will be included.
Studies involving the addition of the following LAMAs at any dose will be included:

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

Eligable comparison groups will be randomised to receive the same dose of ICS as the intervention group, with the addition of any of the following LABAs:

- Formoterol 12 or 24 mcg twice daily
- Salmeterol 50 mcg twice daily
- Vilanterol 22 mcg once daily

Since LABAs are available as single inhalers or in combination inhalers with ICS (e.g. Symbicort, Seretide, Dulera, Relvar), we will include either as long as the ICS is comparable to the dose given alongside the LAMA in the intervention group.
We will include studies that allow participants to continue using their usual short- or long-acting medications (e.g. salbutamol, terbutaline and ipratropium, leukotriene receptor antagonists), provided any non-randomised LAMA or LABA were stopped during the study run-in.

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. Any serious adverse event

Secondary outcomes

1. Exacerbations requiring hospitalisation
2. Lung function (in particular, trough FEV1)
3. Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire or Asthma Control Test)
4. Any adverse events

Reporting one of more of the outcomes listed here in the trial is not an inclusion criterion for the review.
If exacerbations are reported as a composite of more than one definition (e.g. patients with one or more exacerbation requiring hospitalisation *or* ED visit), we will analyse these separately.

Search methods for identification of studies

Electronic searches

We will identify trials from the Cochrane Airways Group's 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, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR using the search strategy in Appendix 2. We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information.

We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (KK and DE) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (KK and DE) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (DA or AB). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Two review authors (KK and DE) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: 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) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data was not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (DA or AB). One review author (KK) will transfer data into the Review Manager (RevMan) file. We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (DE) will spot-check study characteristics for accuracy against the trial reports.

Assessment of risk of bias in included studies

Two review authors (KK and DE) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (DA or AB). We will assess the risk of bias 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 will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider 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 relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We will enter data presented as a scale with a consistent direction of effect. We will narratively describe skewed data reported as medians and interquartile ranges. We will analyse data from crossover trials using generic inverse variance (GIV) and only if double-counting of participants has been accounted for. If raw data and adjusted analyses (e.g. accounting for baseline differences) are both presented, we will use the latter.

We will undertake 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 are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

If change from baseline and endpoint scores are available for continuous data, we will use change from baseline unless the majority of studies report endpoint scores. If a study reports outcomes at multiple time-points, we will use the end-of-study measurement. When an analysis using only participants who completed the trial and an analysis which imputes data for participants who were randomised but did not provide endpoint data (e.g. last observation carried forward) are both available, we will use the latter.

For dichotomous outcomes, we will assume equivalence of treatments if the odds ratio estimate and its 95% confidence intervals are between the pre-defined arbitrary limits of 0.9 and 1.1.

Unit of analysis issues

For dichotomous outcomes, we will use 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 are reported as rate ratios we will analyse them on this basis.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results using a sensitivity analysis**.**

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (e.g. I^2 greater than 30%) we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We will use a random-effects model for all analyses as we expect variation in effects due to differences in study populations and methods. We will perform sensitivity analyses with fixed-effects.

Summary of findings table

We will create a 'Summary of findings' table for all outcomes named in this protocol. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use 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). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

Where possible, we plan to carry out the following subgroup analyses for the primary outcomes, using the formal test for subgroup differences in Review Manager (version 5.3) (Review Manager (RevMan)):

1. Duration of therapy ($\leq$ 6 months, > 6 months)
2. Corticosteroid dose (according to GINA 2014-defined low, medium and high cut-offs)
3. Dose and type of LABA (e.g. formoterol 24 mcg, salmeterol 50 mcg)
4. Dose and type of LAMA (e.g. tiotropium HandiHaler 18 mcg, tiotropium respimat 5 mcg)

Sensitivity analysis

We plan to carry out sensitivity analyses for the primary outcomes by excluding the following:

1. Studies at high risk of bias for blinding of participants and personnel
2. Unpublished data (i.e. no peer-reviewed full paper available)
3. Cross-over trials

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Disclaimer: The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the NIHR, the NHS or the Department of Health.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*the Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Hand-searches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.

6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant trials from the CAGR

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 Muscarinic* NEXT Antagonist*
#6 LAMA:TI,AB
#7 Glycopyrronium*
#8 NVA237
#9 Seebri OR Breezhaler
#10 Aclidinium*
#11 LAS34273
#12 Turdorza or Pressair or Eklira or Genuair
#13 tiotropium*
#14 Spiriva
#15 umeclidinium*
#16 GSK573719
#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 MeSH DESCRIPTOR Adrenergic beta-Agonists
#19 long* NEAR beta* NEAR agonist*
#20 LABA:TI,AB
#21 *formoterol
#22 salmeterol
#23 vilanterol

#24 #18 or #19 or #20 or #21 or #22 or #23
#25 #4 and #17 and #24
[Note: in search line #1, MISC2 denotes the field in which the reference has been coded for condition, in this case, asthma]

CONTRIBUTIONS OF AUTHORS

Kayleigh Kew wrote the background and methods, with edits and critical input from Debbie Allison, Anne Boyter and David Evans. 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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Evidence to guide care in adults and children with asthma, 13/89/14