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Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma (Review)

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[Intervention Review]

Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma

Iain Crossingham[1], Sally Turner[2], Sanjay Ramakrishnan[3], Gareth Hynes[4], Matthew Gowell[5], Farhat Yasmin[6], Anastasia Fries[4], Adnan Chaudhry[7], Timothy SC Hinks[4,8]

[1]East Lancashire Hospitals NHS Trust, Blackburn, UK. [2]Respiratory Assessment Unit, Royal Blackburn Hospital, ELHT, Blackburn, UK. [3]Experimental Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, UK. [4]Respiratory Medicine Unit, Nuffield Department of Medicine, University of Oxford, Oxford, UK. [5]New College, Oxford, University of Oxford Medical School, Oxford, UK. [6]Pharmacy, University Hospitals of Leicester NHS Trust, Leicester, UK. [7]Department of Respiratory Medicine, East Lancashire Hospitals, Blackburn, UK. [8]NIHR Oxford Biomedical Research Centre, Nuffield Department of Medicine, University of Oxford, Oxford, UK

Contact address: Iain Crossingham, East Lancashire Hospitals NHS Trust, Blackburn, Lancashire, UK. Iain.crossingham@elht.nhs.uk.

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ABSTRACT

There is no abstract. The objectives are as follows:

To evaluate the efficacy and safety of single combined (long- or short-acting beta$_2$ agonist plus an inhaled corticosteroid (ICS)) inhaler only used as needed in people with mild asthma.

BACKGROUND

Description of the condition

Asthma is the most common chronic respiratory disease, affecting 350 million people worldwide; and it is potentially serious, claiming 400,000 lives per year (GBD Study 2017; GINA 2019). Asthma is recognised as a heterogeneous disease, but common symptoms include wheezing, shortness of breath, chest tightness and cough; these vary over time in their occurrence, frequency and intensity (GINA 2019). Asthma is a clinical diagnosis defined by the history of a constellation of respiratory symptoms that vary over time and in intensity, together with variable expiratory airflow limitation (GINA 2019). Asthma treatment broadly focusses on maintaining daily symptom control and preventing acute worsening of symptoms known as asthma attacks or 'exacerbations'.

The seriousness of asthma varies greatly and severe asthma has attracted significant interest from researchers. Asthma control is the extent to which features of asthma are observed in an individual or have been reduced by treatment. Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations (GINA 2019). Globally, prevalence of mild asthma is estimated to be between 45% and 70% of all patients diagnosed with the condition (Rabe 2004; Dusser 2007; Sadatsafavi 2010). Despite being labelled as having mild asthma, this group continues to have severe asthma attacks requiring oral steroids or hospital admission (Bloom 2018), and suffer asthma-related deaths (Bergström 2008; RCP 2014). Inhaled corticosteroids (ICS) are the most effective preventer drug for adults in achieving overall treatment goals and reducing mortality (Suissa 2000). Intermittence of symptoms in this population often leads to poor inhaler adherence (Taylor 2014). Up to 90% of people with asthma do not take ICS regularly as prescribed (AIHW 2007). Poor adherence to preventer ICS is thought to be a main cause for increase in risk of exacerbations in people with mild asthma (Engelkes 2015).

Description of the intervention

Preventers and relievers

There are over 30 different inhalers now approved for use in asthma. They are usually classified as preventers or relievers. Short-acting beta agonists (SABA) have been used since the 1970s for rapid relief of asthma symptoms from bronchoconstriction. They lead to rapid improvement of symptoms but do not affect the underlying pathological process (Barnes 1999).

Taking daily preventer steroid inhalers should lead to better asthma control (Chauhan 2013). Adherence to inhaled steroids is often poor, however, for a variety of reasons including fear of side effects, costs and perceptions of asthma severity (Bender 2005). Increasing the daily dose of the preventer ICS therapy during the early phase of an acute exacerbation has also been studied as a way to treat the exacerbation without the need for systemic corticosteroids (Kew 2016), though a benefit from this approach has not been shown. These regimes still depend on the use of a preventer even when the patient feels well; and they are still affected by poor adherence rates (Beasley 2019).

Longer-acting beta$_2$ agonists (LABA) are also available. They are generally used as preventer medication and are co-prescribed with an ICS. Some LABAs have a rapid onset of action and will also rapidly relieve symptoms (Wallin 1993).

Fixed dose combination inhalers

A number of combination inhalers exist. These contain both a steroid and a beta$_2$ agonist in the same device, thus delivering both treatments at the same time. This has the advantages of simplifying an inhaler regime and ensuring LABA therapy is not taken without ICS. This is important because use of a LABA without an ICS is associated with a significantly increased risk of asthma death (Nelson 2006).

Exacerbations or 'attacks' are thought to be precipitated by external triggers (viral, bacterial, allergen or irritants) leading to an enhanced type 2 inflammatory response in the asthmatic airways (Papi 2018). The prodrome preceding an attack would be a logical time to intervene, especially if these are infrequent. The rapid-acting beta$_2$ agonist will act immediately on the smooth muscle to relieve airway narrowing and resultant symptoms. ICS are thought to work by suppressing the type 2 inflammation at the epithelial level (Barnes 2010). Pairing the ICS with the beta$_2$ agonist therapy, specifically at the time of increased symptoms, could lead to both symptomatic improvement and suppression of the underlying pathological process, and importantly decrease the risk of severe or life-threatening events (Beasley 2019). In patients with moderate asthma not controlled on medium-dose ICS or ICS/LABA, fixed-dose ICS/LABA inhalers used as both maintenance and reliever therapy (MART) is effective in reducing risk of asthma attacks (Cates 2013), but these data cannot necessarily be extrapolated to mild asthma or to use of the combination inhaler as required, without its use also as regular maintenance therapy.

How the intervention might work

This review will focus on fixed-dose combination ICS/rapid onset beta$_2$ agonist taken as needed — i.e. both treatments in the same inhaler. This is now being considered as a replacement for prescribing people either a SABA or SABA and a separate ICS. The idea is that when people's symptoms are worse they will take their inhaler more often to get symptom relief from the bronchodilator (Wallin 1993); and they will also get more steroid to treat the underlying inflammation (Barnes 2010). This also has the possible benefit of simplification due to the use of a single inhaler as well as reduced issues with adherence, and may in effect titrate the amount of ICS delivered to the individual's symptomatology.

Why it is important to do this review

Several clinical trials of as-required fixed-dose combination inhalers have reported in recent years, and have led to a significant change in an international guideline (GINA 2019), which now recommends fixed-dose ICS/rapid-acting beta$_2$ agonist as first line therapy for mild asthma, where the previous guideline recommended use of SABA only. As the majority of economic costs of asthma are related to regular prescribing of preventer medications in primary care (Mukherjee 2016), this recommendation has major cost implications, particularly for public health systems in low- to middle-income countries. There is also the potential for important benefits in improving symptom control, reducing exposure to systemic corticosteroids and reducing admissions — the last of which is a major contributor to the economic burden of asthma (Mukherjee 2016). Therefore an accurate assessment of these benefits using all available randomised clinical trial data is timely, with implications for millions of people with asthma worldwide.

OBJECTIVES

To evaluate the efficacy and safety of single combined (long- or short-acting beta$_2$ agonist plus an inhaled corticosteroid (ICS)) inhaler only used as needed in people with mild asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include cross-over designs provided they include an appropriate washout period (a week or more) between interventions. We will include cluster randomised trials if the data have been or can be adjusted for clustering. We will exclude trials of very short duration (an intervention of less than 12 weeks). We will include studies reported in full text, those published as an abstract only and unpublished data.

Types of participants

We will include adults and children (age 6 years and older) with a diagnosis of mild asthma as defined by GINA 2019: asthma that is well controlled with as-needed controller medication alone, or with low-intensity maintenance controller treatment. Where GINA definitions are not specified, authors will judge severity using baseline characteristics, requiring an Asthma Control Questionnaire (ACQ) score less than or equal to 1.5 or an Asthma Control Test (ACT) score equal to or more than 16. We will not exclude participants based on non-respiratory co-morbidities, provided they also meet the required definition for a diagnosis of asthma. We will exclude participants with chronic obstructive pulmonary disease (COPD), defined by GOLD 2020; and any physician diagnosis of pulmonary fibrosis, bronchiectasis, lung cancer or other respiratory co-morbidity. To ensure that we are only investigating patients with mild asthma, we will exclude patients taking moderate-dose ICS daily (defined as greater than or equal to 300 µg per day of beclomethasone equivalent) or higher-dose ICS daily (defined as greater than or equal to 600 µg per day of beclomethasone equivalent for adults and children aged 12 years or older).

Types of interventions

We will include studies comparing a single fixed-dose ICS/rapid onset beta$_2$ agonist inhaler used as needed with at least one of the following comparators.

1. No treatment
2. Placebo
3. As-required SABA
4. Regular ICS with as-required SABA
5. Regular fixed-dose combination ICS/LABA, with or without as-required SABA
6. Regular fixed-dose combination ICS/LABA with as-required ICS/LABA

Separate comparisons will be done comparing single fixed-dose ICS/rapid onset beta$_2$ agonist inhaler against each of the comparators listed above. Rapid onset beta$_2$ agonists include salbutamol (albuterol), terbutaline, and formoterol.

We will not consider studies investigating other asthma treatments: if required, they would suggest severe asthma. This will include systemic corticosteroids, leukotriene inhibitors, inhaled long-acting anti-cholinergics, methylxanthines and monoclonal antibodies.

Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies. Where possible we will analyse outcomes at the 12-month time point.

Primary outcomes

1. Exacerbations requiring systemic steroids.
2. Hospital admissions/emergency department or urgent care visits for asthma.
3. Measures of asthma control: in order of preference Asthma Control Questionnaire, Asthma Control Test, symptom-free days.

Secondary outcomes

1. Measures of lung physiology: in order of preference post-bronchodilator FEV_1, post-bronchodilator PEFR, FeNO, then other measures.
2. Quality of life measures, preferably Asthma Quality of Life Questionnaire, then SF-36.
3. Adverse events/side effects.
4. Total inhaled steroid dose. We will convert inhaled steroid doses to beclomethasone equivalents using the conversion described in Table 1.
5. Total systemic corticosteroid dose.
6. Mortality.

Search methods for identification of studies

Electronic searches

We will identify studies from searches of the following databases and trial registries.

1. Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, all years to date.
2. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, via the Cochrane Register of Studies, all years to date.
3. MEDLINE Ovid SP 1946 to date.
4. Embase Ovid SP 1974 to date.
5. US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov).
6. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We present the proposed MEDLINE search strategy in Appendix 1. This will be adapted for use in the other databases. The search strategy was developed by the Cochrane Airways Information Specialist in collaboration with the authors, and was peer-reviewed by another Cochrane Information Specialist using the PRESS checklist (McGowan 2016).

We will search all databases and trials registries from their inception to the present, and we will impose no restriction regarding

language or type of publication. We will identify handsearched conference abstracts and grey literature through the Cochrane Airways Trials Register and the CENTRAL database.

Searching other resources

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

We will search on PubMed for errata or retractions from included studies published in full text, and report the date this was done within the review.

Data collection and analysis

Selection of studies

We plan to use Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and have been labelled as 'RCT' or 'Not an RCT'; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs; and, if appropriate, Cochrane Crowd (crowd.cochrane.org) – Cochrane's citizen science platform where 'the crowd' help to identify and describe health evidence. More detailed information about the Screen4Me components can be found in the following publications: McDonald 2017; Thomas 2017; Marshall 2018; Noel-Storr 2018.

Following this initial assessment, four review authors (ST, FY, MG, AF) will screen the titles and abstracts of the remaining search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve', with each abstract being screened by at least two authors. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (two of ST, FY, MG and AF) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person/review author (IC or TSCH). 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 (Moher 2009).

Data extraction and management

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

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 (including types and doses of beta agonist and corticosteroid), concomitant medications, prior medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (SR, GH) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by discussion or by involving a third person/review author (IC or TSCH) to reach consensus. One review author (IC) will transfer data into the Review Manager 5 file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (TSCH) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SR, GH) will assess risk of bias independently for each study using the criteria outlined in version 5.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (IC or TSCH). 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 judge each potential source of bias as high, low or unclear risk and provide a quote from the study report together with a justification for our judgement 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.

Assessment of bias in conducting the systematic review

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

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) or (where appropriate) rate ratios (RR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). If data from rating scales are combined in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement).

We will undertake meta-analyses only where this is meaningful: that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

Where multiple trial arms are reported in a single study, 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 either combine the active arms or halve the control group to avoid double-counting.

If adjusted analyses are available (ANOVA or ANCOVA) we will use these as a preference in our meta-analyses. If both change from baseline and endpoint scores are available for continuous data, we will use change from baseline unless there is low correlation between measurements in individuals. If a study reports outcomes at multiple time points, we will use 12 months preferentially, with 3 months as a 'second choice'.

We will use intention-to-treat (ITT) or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per protocol analyses

Unit of analysis issues

For outcomes involving event counts where participants may have multiple events (exacerbations, hospitalisations) and 3 or 12 month incidence rates are available, we will use events primarily as the unit of analysis rather than participants. For other dichotomous outcomes and where incidence rate ratios are not available, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted) to account for the clustering.

Where possible, we will include data from paired analyses of any identified cross-over studies.

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 an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, 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 and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes.

- Exacerbations requiring systemic steroids
- Hospital admissions/emergency department or urgent care visits for asthma
- Asthma control, preferably measured by the Asthma Control Questionnaire
- Inhaled steroid dose
- Total systemic steroid dose
- Adverse events

We will use the five GRADE considerations (risk of bias; consistency of effect; imprecision; indirectness; and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Adults and adolescents vs children (i.e. 12 years and over vs under 12 years) in keeping with GINA 2019 definitions
2. High vs low eosinophils (for trials where this is reported, using the trialists' definition of high and low)
3. High vs low FeNO (where reported, using the trialists' definition of high and low)
4. By inhaler component drugs (i.e. by each inhaled steroid drug and by short- or long-acting beta agonist)

We will use the following outcomes in subgroup analyses.

1. Exacerbations requiring oral steroid
2. Hospital admissions/emergency department or urgent care visits for asthma
3. Measures of asthma control

We will use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2014).

Sensitivity analysis

We plan to carry out sensitivity analyses, removing the following from the primary outcome analyses.

1. Trials deemed at high risk of bias in at least one domain
2. Cross-over (as opposed to parallel group) trials
3. Trials in which asthma severity is not explicitly stated, but only derived from baseline characteristics

We will compare the results from a fixed-effect model with the random-effects model.

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REFERENCES

Additional references

AIHW 2007

Australian Institute of Health and Welfare. Asthma in Australia with a focus chapter on chronic obstructive pulmonary disease. www.aihw.gov.au/getmedia/8d7e130c-876f-41e3-b581-6ba62399fb24/11774.pdf.aspx?inline=true (accessed prior to 20 September 2019).

Barnes 1999

Barnes PJ. Effect of beta-agonists on inflammatory cells. *Journal of Allergy and Clinical Immunology* 1999;**104**(2 Pt 2):S10-17. [PUBMED: 10452784]

Barnes 2010

Barnes PJ. Inhaled corticosteroids. *Pharmaceuticals* 2010;**8**(3):514-40. [PUBMED: 27713266]

Beasley 2019

Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Novel START Study Team. Controlled trial of budesonide-formoterol as needed for mild asthma. *New England Journal of Medicine* 2019;**380**(21):2020-30. [PUBMED: 31112386]

Bender 2005

Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunology and Allergy Clinics of North America* 2005;**25**(1):107-30. [PUBMED: 15579367]

Bergström 2008

Bergström SE, Boman G, Eriksson L, Formgren H, Foucard T, Hörte L.G, et al. Asthma mortality among Swedish children and young adults, a 10-year study. *Respiratory Medicine* 2008;**102**(9):1335-41. [PUBMED: 18635346]

Bloom 2018

Bloom CI, Nissen F, Douglas IJ, Smeeth L, Cullinan P, Quint JK. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax* 2018;**73**(4):313. [PUBMED: 29074814]

Cates 2013

Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children.. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: 10.1002/14651858.CD007313.pub3; PUBMED: 23633340]

Chauhan 2013

Chauhan BF, Chartrand C, Ducharme FM. Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. *Cochrane Database of Systematic Reviews* 2013, Issue 2. [DOI: 10.1002/14651858.CD009611.pub3; CD009611]

Cochrane Airways 2019

Cochrane Airways Trials Register. airways.cochrane.org/trials-register (accessed 7 May 2019).

Dusser 2007

Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. *Allergy* 2007;**62**(6):591-604. [PUBMED: 17508962]

Engelkes 2015

Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MCJM, Verhamme KMC. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *European Respiratory Journal* 2015;**45**(2):396. [PUBMED: 25323234]

GBD Study 2017

Global Burden of Disease Study. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respiratory Medicine* 2017;**5**(9):691-706. [PUBMED: 28822787]

GINA 2019

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (2019 update). ginasthma.org/reports/ (accessed prior to 20 September 2019).

GOLD 2020

Global Strategy for Prevention, Diagnosis and Management of COPD 2020 Report. goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.1wms.pdf (accessed 4th December 2019).

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 16 October 2019. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Higgins 2019

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook..

Kew 2016

Kew KM, Quinn M, Quon BS, Ducharme FM. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. *Cochrane*

Database of Systematic Reviews 2016, Issue 6. [DOI: 10.1002/14651858.CD007524.pub4; PUBMED: 27272563]

Marshall 2018

Marshall IJ, Noel-Storr AH, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials: an evaluation and practitioner's guide. *Research Synthesis Methods* 2018;**9**(4):602-14.

McDonald 2017

McDonald S, Noel-Storr AH, Thomas J. Harnessing the efficiencies of machine learning and Cochrane Crowd to identify randomised trials for individual Cochrane reviews. Global Evidence Summit; 2017 September 13-16; Cape Town, South Africa. 2017.

McGowan 2016

McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *Journal of Clinical Epidemiology* 2016;**75**:40-6. [DOI: 10.1016/j.jclinepi.2016.01.021]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097. [DOI: 10.1371/journal.pmed.1000097]

Mukherjee 2016

Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Medicine* 2016;**14**(1):113. [PUBMED: 27568881]

Nelson 2006

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol.. *Chest* 2006;**129**(1):15-26.

Noel-Storr 2018

Noel-Storr AH, Project Transform team. Cochrane Crowd: new ways of working together to produce health evidence. Evidence Live; 2018 June 18-20; Oxford, UK. 2018.

Papi 2018

Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018;**391**(10122):783-800. [PUBMED: 29273246]

Rabe 2004

Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *Journal of Allergy and Clinical Immunology* 2004;**114**(1):40-7. [PUBMED: 15241342]

RCP 2014

Royal College of Physicians. The National Review of Asthma Deaths. www.rcplondon.ac.uk/projects/national-review-asthma-deaths (accessed prior to 20 September 2019).

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sadatsafavi 2010

Sadatsafavi M, Lynd L, Marra C, Carleton B, Tan WC, Sullivan S, et al. Direct health care costs associated with asthma in British Columbia. *Canadian Respiratory Journal [Revue Canadienne de Pneumologie]* 2010;**17**(2):74-80. [PUBMED: 20422063]

Suissa 2000

Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *New English Journal of Medicine* 2000;**343**(5):332-6. [PUBMED: 10922423]

Taylor 2014

Taylor A, Chen LC, Smith MD. Adherence to inhaled corticosteroids by asthmatic patients: measurement and modelling. *International Journal of Clinical Pharmacy* 2014;**36**(1):112-19. [PUBMED: 24293333]

Thomas 2017

Thomas J, Noel-Storr AH, Marshall I, Wallace B, McDonald S, Mavergames C, et al. Living systematic review network. Living systematic reviews: 2. Combining human and machine effort. *Journal of Clinical Epidemiology* 2017;**91**:31-7.

Wallin 1993

Wallin A, Sandström T, Rosenhall L, Melander B. Time course and duration of bronchodilatation with formoterol dry powder in patients with stable asthma. *Thorax* 1993;**48**(6):611-4. [PUBMED: 8346490]

ADDITIONAL TABLES

Table 1. Inhaled steroid equivalents

Drug	Dose considered equivalent to 100 µg beclomethasone dipropionate	Conversion factor
Beclometasone	100	1.0
Beclometasone (extra fine particles)	50	2.0

Table 1. Inhaled steroid equivalents *(Continued)*

Budesonide	100	1.0
Fluticasone propionate	50	2.0
Fluticasone furoate	12.5	8.0
Mometasone	50	2.0
Ciclesonide	62.5	1.6

APPENDICES

Appendix 1. Database search strategy

Ovid MEDLINE(R) ALL <1946 to September 13, 2019>

Searches

1 exp Asthma/

2 asthma$.ti,ab.

3 1 or 2

4 Fluticasone/

5 Budesonide/

6 Beclomethasone/

7 exp Triamcinolone/

8 fluticasone.tw.

9 beclomethasone.tw.

10 budesonide.tw.

11 triamcinolone.tw.

12 flunisolide.tw.

13 ciclesonide.tw.

14 (flixotide or flovent).tw.

15 (becotide or beclofort or becodisk or QVAR or vanceril).tw.

16 pulmicort.tw.

17 (kenalog or azmacort).tw.

18 bronalide.tw.

19 Alvesco.tw.

20 Mometasone Furoate/

21 mometasone.tw.

22 (inhal$ adj3 (steroid$ or corticosteroid$ or glucocorticoid$)).tw.

23 or/4-22

24 exp Adrenergic beta-2 Receptor Agonists/

25 exp Albuterol/

26 Terbutaline/

27 Formoterol Fumarate/

28 Salmeterol Xinafoate/

29 (Salbutamol or albuterol).tw.

30 Terbutaline.tw.

31 Bambuterol.tw.

32 (formoterol or eformoterol).tw.

33 Indacaterol.tw.

34 Olodaterol.tw.

35 salmeterol.tw.

36 or/24-35

37 Fluticasone-Salmeterol Drug Combination/

38 Budesonide, Formoterol Fumarate Drug Combination/

39 Mometasone Furoate, Formoterol Fumarate Drug Combination/

40 Fostair.tw.

41 Symbicort.tw.

42 DuoResp Spiromax.tw.

43 Fobumix.tw.

44 Seretide.tw.

45 Relvar.tw.

46 Ventide.tw.

47 Aerocort.tw.

48 Salbair.tw.

49 or/37-48

50 23 and 36

51 3 and (49 or 50)

52 (controlled clinical trial or randomized controlled trial).pt.

53 (randomized or randomised).ab,ti.

54 placebo.ab,ti.

55 dt.fs.

56 randomly.ab,ti.

57 trial.ab,ti.

58 groups.ab,ti.

59 or/52-58

60 Animals/

61 Humans/

62 60 not (60 and 61)

63 59 not 62

64 51 and 63

CONTRIBUTIONS OF AUTHORS

SR and TSCH wrote the protocol background. IC wrote the Methods section based on a standard Cochrane template with contributions from all the authors.

Contributions of editorial team

1. Rebecca Fortescue (Co-ordinating Editor): edited the protocol; advised on methodology.
2. Chris Cates (Co-ordinating Editor): checked the planned methods, approved the protocol prior to publication.
3. Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on content; edited the protocol.
4. Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references.
5. Elizabeth Stovold (Information Specialist): designed the search strategy; arranged for peer review of the search strategy.

DECLARATIONS OF INTEREST

1. I Crossingham works in a clinically relevant speciality. He has been involved in recruitment for a GlaxoSmithKline-sponsored trial of inhaled nemiralisib for COPD, but did not directly receive funding for this. In February 2017 Hamilton Medical paid for his travel and accommodation to attend training on their ventilators as part of a post-sales package to his institution. Ventilation is a potential supportive therapy for acute severe asthma but not directly relevant to this review.
2. TSC Hinks has received research funding from the Wellcome Trust (4 February 2015 to 31 July 2018, 3 December 2018 – ongoing), NIHR (1 May 2019 – ongoing), and the Beit Guardians (3 December 2018 – ongoing). He has received speaker fees from AstraZeneca in June 2019, Boehringer Ingelheim (March 2019) and his research team have received funding from Sanofi (September 2019 – ongoing).
3. G Hynes has a joint research fellowship from the University of Oxford and UCB. He has attended educational events sponsored by Sanofi (September 2019), Teva (2018) and AstraZeneca (2016 and 2017), and has received an honorarium from Teva in 2018 for producing educational materials over which Teva had no editorial control.
4. F Yasmin has no relevant conflicts of interest.
5. A Fries works in a clinically relevant speciality.
6. S Ramakrishnan is undertaking a PhD supported by an unrestricted research grant from AstraZeneca. He has attended educational events sponsored by AstraZeneca (2019). He also works in a clinically relevant specialty.
7. M Gowell has no relevant conflict of interest.
8. S Turner reports money for travel from Novartis in 2019 for an educational event.
9. A Choudhry works in a clinically relevant speciality.

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