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EXAMINER

[Intervention Review]

Focused review format prototype

Ella Flemyng¹, Denise Mitchell¹

¹Cochrane, London, UK

Contact: Ella Flemyng, eflemyng@cochrane.org.

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ABSTRACT

Rationale

Early treatment of asthma exacerbations with inhaled corticosteroids is the best strategy for management, although use of an increased or stable dose is questioned.

Objectives

To compare the clinical effectiveness and safety of increased versus stable doses of inhaled corticosteroids as part of a patient-initiated action plan for the home management of exacerbations in children and adults with persistent asthma.

Search methods

We searched the Cochrane Airways Group Specialised Register (part of CENTRAL), MEDLINE, Embase, CINAHL, major trials registries and handsearched abstracts up to 20 December 2021.

Eligibility criteria

Parallel and cross-over blinded randomised controlled trials (RCTs).

Outcomes

Treatment failure (the need for rescue oral steroids) in the randomised population and in the subset who initiated the study inhaler, unscheduled physician visits, unscheduled acute care, emergency department or hospital visits, serious and non-serious adverse events, and duration of exacerbation.

Risk of bias

We used Risk of Bias 2 (RoB 2) and the tool's extension for cross-over trials.

Synthesis methods

We conducted meta-analyses using fixed-effect models to calculate odds ratios (OR) and 95% confidence intervals (CI) for all but one outcome, which used random-effects models due to heterogeneity (treatment failure in the subset who initiated the study inhaler). We summarised certainty of evidence according to GRADE methods.

Included studies

We included nine RCTs (seven parallel and two cross-over) with a total of 1923 participants. The studies were conducted in Europe, North America, and Australasia and were published between 1998 and 2018. Five studies evaluated adult populations (1247 participants; ≥ 15 years), and four studies evaluated child or adolescent populations (676 participants; < 15 years). Approximately 50% of randomised participants initiated the study inhaler (range 23% to 100%). The studies reported treatment failure in various ways, so we made assumptions to allow us to combine data.

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Synthesis of results

People randomised to increase their inhaled corticosteroids dose at the first signs of an exacerbation probably had similar odds of needing rescue oral corticosteroids to those randomised to a placebo inhaler (OR 0.97, 95% CI 0.76 to 1.25; 8 studies, 1774 participants; moderate-certainty evidence). Results for the same outcome in the subset of participants who initiated the study inhaler (approximately 50%) gives a different point estimate with very low certainty due to heterogeneity, imprecision and risk of bias (OR 0.84, 95% CI 0.54 to 1.30; 7 studies, 766 participants; random-effects model used). For adverse effects, imprecision and risk of bias from missing data, outcome measurement and reporting meant we were very uncertain about the effect estimate (serious adverse events OR 1.69, 95% CI 0.77 to 3.71; 2 studies, 394 participants; non-serious adverse events OR 2.15, 95% CI 0.68 to 6.73; 2 studies, 142 participants). We had very low confidence in the effect estimates for unscheduled physician visits, unscheduled acute care, emergency department or hospital visits and duration of exacerbation due to risk of bias.

Authors' conclusions

Evidence suggests that adults and children with mild to moderate asthma are unlikely to have an important reduction in the need for oral steroids from increasing a patient's inhaled corticosteroid dose at the first sign of an exacerbation. Other clinically important benefits and potential harms cannot be ruled out due to wide confidence intervals, risk of bias in the studies, and assumptions made for synthesis when combining data. Included studies reflect evolving clinical practice and study methods, and the data do not support thorough investigation of effect modifiers such as baseline dose, fold increase, asthma severity and timing. The review does not include recent evidence from pragmatic, unblinded studies showing benefits of larger dose increases in those with poorly controlled asthma. Differences between the blinded and unblinded studies should be investigated.

Funding

This Cochrane Review had no dedicated funding.

Registration

Protocol (2009): doi.org/10.1002/14651858.CD007524

Original review (2010): doi.org/10.1002/14651858.CD007524.pub3

Review update (2014): doi.org/10.1002/14651858.CD007524.pub4

PLAIN LANGUAGE SUMMARY

Is increasing the dose of inhaled steroids to treat asthma attacks in adults and children more effective than continuing the usual dose?

Key messages

- Adults and children with mild to moderate asthma, who follow an action plan to take an inhaler containing an increased dose of corticosteroids at the first sign of an asthma attack, are probably as likely to worsen and need oral steroids as people who continue their normal dose.
- We don't know whether taking an increased dose of inhaled corticosteroids at the first sign of an asthma attack helps to reduce unwanted effects, emergency visits to the doctor or hospital, or the length of the asthma attack.
- We only looked at studies where people did not know what dose of corticosteroids their inhaler contained. Studies that did not hide the dose in the inhaler showed better results for an increased dose. We need to investigate the effect of hiding or not hiding the dose.

What is asthma, and how is it treated?

Asthma is a common, long-term lung condition that causes cough, shortness of breath and wheezing. Most people with asthma have a written plan to help them control their symptoms and help them deal with an asthma attack. People with asthma often use an inhaler every day to control their symptoms. This contains medication called corticosteroids. If necessary, they may be given emergency treatment with a stronger dose of corticosteroids. These may be inhaled (the medication goes directly to the lungs) or swallowed (oral corticosteroids, which affect the whole body).

Why is this important for people with asthma?

Asthma attacks can be frightening, life-threatening, and often require urgent treatment at home or in hospital. Short term, oral corticosteroids may cause disturbed sleep, increased appetite and mood changes. Over time, they may cause problems with bone strength, high blood pressure, diabetes and obesity. Using a higher dose of inhaled corticosteroids as soon as signs of an asthma attack appear might prevent the attack and avoid hospital treatment and taking oral corticosteroids.

What did we want to find out?

We wanted to know how many people who received an increased inhaled corticosteroid dose would have an asthma attack, and if there were any unwanted effects. We were also interested in the effect on unplanned visits to the doctor or emergency department, stays in hospital, and how long the attacks lasted.

What did we do?

We searched for studies that compared continuing a normal dose of inhaled corticosteroids with an increased dose, at the first sign of an asthma attack, as part of an asthma action plan. Studies had to choose people at random for the increased or normal dose and ensure people didn't know which dose they were receiving. Studies could investigate adults or children with mild to moderate asthma.

We compared and summarised the study results, and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 9 studies with 1923 people; 5 studies with adults and 4 with children. Studies took place in Europe, North America and Australasia.

- Based on all the participants, 180 out of 1000 people with the increased dose would need oral corticosteroids compared to 184 people out of 1000 on their normal dose. So, people taking the increased dose of inhaled corticosteroid were probably as likely to get worse and need oral corticosteroids as those taking their usual dose.
- About half of the participants used their inhaler at the first signs of an asthma attack. Of these, people with the increased-dose inhalers may be slightly less likely to need oral corticosteroids than those on their normal dose.
- We don't know whether an increased dose of inhaled corticosteroids makes a difference to unwanted effects - they occurred with increased and normal doses of inhaled corticosteroids. Examples include bronchitis, viral meningitis and upper respiratory tract infection.
- We don't know whether an increased dose of inhaled corticosteroids makes a difference to unplanned visits to the doctor or to the emergency department; stays in hospital; or how long the asthma attack lasts.

What are the limitations of the evidence?

Our confidence in the evidence is moderate to very low for several reasons. Studies varied in the daily dose of inhaled corticosteroids people were taking at the start of the study, how much they increased the dose, when and how people were told to start the inhaler, and what other medicines they were allowed to take. Also, studies showed different results, and did not report unwanted effects in the same way. Thankfully not many people needed to go to hospital or visit the emergency department while they were in the studies, but this made it difficult to tell if a short-term increase in inhaled corticosteroids is worthwhile.

How up to date is this evidence?

The review is current to 20 December 2021. The studies were published over a 20-year period from 1998 to 2018.

SUMMARY OF FINDINGS
Summary of findings 1. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children
Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children

Patient or population: adults and children with chronic asthma
Setting: outpatient
Intervention: increased ICS dose at first signs of exacerbation
Comparison: stable ICS dose at first signs of exacerbation

Outcomes*	Anticipated absolute effects** (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE) ^a
	Risk with stable ICS	Risk with increased ICS			
Treatment failure: need for systemic corticosteroids (ITT) 46 weeks	184 per 1000^b	180 per 1000 (147 to 220)	OR 0.97 (0.76 to 1.25)	1774 (8 RCTs)	⊕⊕⊕⊖ Moderate ^c
Treatment failure: need for systemic corticosteroids (of those starting in-haler) 45 weeks	337 per 1000	299 per 1000 (215 to 398)	OR 0.84 (0.54 to 1.30)	766 (7 RCTs)	⊕⊖⊖⊖ Very low ^{d,e}
Unscheduled physician visits 44 weeks	147 per 1000	142 per 1000 (102 to 195)	OR 0.96 (0.66 to 1.41)	931 (3 RCTs)	⊕⊖⊖⊖ Very low ^{f,g,h}
Unscheduled acute care, ED visit, or hospital admission 47 weeks	23 per 1000	12 per 1000 (4 to 35)	POR 0.50 (0.16 to 1.56)	704 (4 RCTs)	⊕⊖⊖⊖ Very low ^{f,g,h}
Serious adverse events 48 weeks	56 per 1000	91 per 1000 (44 to 181)	OR 1.69 (0.77 to 3.71)	394 (2 RCTs)	⊕⊕⊖⊖ Low ⁱ
Non-serious adverse events 43 weeks	72 per 1000	144 per 1000 (50 to 345)	OR 2.15 (0.68 to 6.73)	142 (2 RCTs)	⊕⊖⊖⊖ Very low ^{f,j}

<p>Duration of exacerbation - time to symptom recovery and lung function recovery</p> <p>52 weeks</p>	<p>Mean time to symptom recovery was 6.1 days</p> <p>Time to lung function recovery was 7 days.</p>	<p>Time to symptom recovery was 0.7 days longer in the intervention group (1.06 lower to 2.46 higher).</p> <p>Time to lung function recovery was 0.2 days shorter (1.88 shorter to 1.48 longer).</p>	<p>-</p> <p>207 (1 RCT)</p>	<p>⊕⊕⊕⊕ Moderate^{f,d,j}</p>
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*The risk in the intervention group (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).

**Analysed using random-effects models because of heterogeneity.

Follow-up duration is calculated as a weighted average of studies in each meta-analysis.

CI: confidence interval; **ED:** emergency department; **ICS:** inhaled corticosteroids; **ITT:** intention-to-treat population; **OR:** odds ratio; **POR:** Peto odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aFull details about downgrading and upgrading decisions are in [Supplementary material 9](#).

^bAn approximation of Rice-McDonald 2005 events and totals was required because we used cross-over adjustment to include the study in the meta-analysis. We used the total number of participants (18) and events for each arm (11 each), and halved both (rounding up where necessary) to include approximate absolute data and weightings for the study.

^cDowngraded once for risk of bias because studies carrying 13.3% of the meta-analysis weight had overall high risk of bias and studies carrying a further 49.8% of the weight had some concerns.

^dDowngraded once for imprecision as upper and lower confidence intervals include important benefit of increased or stable inhaled corticosteroids.

^eDowngraded once for inconsistency as clear variation noted between direction and magnitude of study results by visual inspection of the forest plot ($I^2 = 42%$, P value = 0.11)

^fDowngraded once for indirectness as outcome definitions or populations used for meta-analysis were unclear or differed from what was defined in the review protocol.

^gDowngraded twice for risk of bias as studies contributing the majority of the weight in both adverse events analyses were at overall high risk of bias.

^hDowngraded once for imprecision as confidence intervals included a significant increase in adverse events on increased dose inhaled corticosteroid and did not exclude the possibility of no difference against stable inhaled corticosteroid. Very few events were included in either of the adverse event analyses.

ⁱDowngraded twice for imprecision as three studies observed 136 events leading to very wide confidence intervals, which made the result very difficult to interpret.

^jDowngraded twice for imprecision as only 12 events in the meta-analysis, leading to a large amount of imprecision in the estimate.

BACKGROUND

Description of the condition

Asthma is the second most prevalent chronic respiratory condition worldwide, and is estimated to affect 272 million people of all ages [1]. According to the Global Burden of Disease Study in 2017, asthma was the second leading cause of death among chronic respiratory diseases [2]. Asthma exacerbations involve short-term, mild to life-threatening worsening of symptoms, which are considered an important feature in defining the severity of the disease [3]. The frequency of exacerbations is a key parameter of asthma control.

Description of the intervention and how it might work

The underlying mechanism of asthma exacerbations is airway inflammation, often triggered by respiratory virus infection, allergen exposure or respiratory irritants [4]. This airway inflammation sets up a vicious cycle of bronchial hyper-responsiveness and mucus hypersecretion, leading to decreased expiratory flow [4]. Acute asthma exacerbations are a medical emergency regardless of age and can be highly dependent on seasonal variation [5].

Systemic corticosteroids have potent anti-inflammatory properties and are the most effective drugs for suppressing the underlying inflammatory response in asthma exacerbations. Common short-term side effects of corticosteroids include sleep disturbances, increased appetite, and mood changes. However, the cumulative impact of chronic corticosteroid use includes a significantly elevated risk of osteoporosis, hypertension, diabetes mellitus, and obesity [6]. This provides a rationale for an alternative management strategy, such as the use of inhaled corticosteroids in mild-to-moderate asthma exacerbation to reduce the need for systemic corticosteroids.

Inhaled corticosteroids can reduce the frequency and severity of respiratory exacerbations [3]. Poor day-to-day asthma control and type 2 airway inflammation, as measured by blood eosinophils or elevated exhaled nitric oxide, are both risk factors for acute exacerbations [7]. Treatment with inhaled corticosteroids remains the cornerstone strategy in the management of chronic asthma.

The Global Initiative for Asthma and other international respiratory societies recommend self-management strategies to reduce the impact of acute exacerbations. A written asthma action plan includes a description of maintenance therapy and instructions for increasing therapy as required. This helps patients to recognise and respond appropriately to worsening symptoms.

The use of short-acting beta agonists helps to relieve the symptoms of asthma by bronchodilation, but does not address the underlying airway inflammation. This can potentially delay seeking medical attention and may increase adverse outcomes in acute asthma [8]. Recent evidence shows the increased risk of exacerbation and mortality with the overuse of short-acting beta agonists [9]. The latest Global Initiative for Asthma report thus no longer recommends reliever treatment with short-acting beta agonists alone [3].

Why it is important to do this review

With the recognition that early treatment of asthma exacerbations is the best strategy for management, the use of inhaled corticosteroids as a part of an action plan is essential. Furthermore, it is important to determine the efficacy of an increased versus stable dose of inhaled corticosteroids in this setting. The critical outcome for this review is treatment failure, defined as the need for rescue systemic corticosteroids. This is an update of the Cochrane Review that was originally published in 2010 [10], and updated in 2016 [11], while incorporating the most recent clinical trials from the literature.

OBJECTIVES

To compare the clinical effectiveness and safety of increased versus stable doses of inhaled corticosteroids as part of a patient-initiated action plan for home management of exacerbations in children and adults with persistent asthma.

METHODS

Since publication of the original protocol in 2009 [12] some methods have been updated (see [Supplementary material 7](#)). In this version, we reassessed all included studies with Risk of Bias 2 (RoB 2) [13, 14] including using the extension for cross-over trials, and elaborated the methods for presenting results and investigating the impact of bias with sensitivity analyses. We also updated the tools used to sift search results, extract data, and conduct analyses to online versions of Covidence [15].

Criteria for considering studies for this review

Types of studies

We included double-blinded (participant- and assessor-blinded), parallel and cross-over randomised controlled trials (RCTs).

Types of participants

We included adults and children with asthma exacerbation as defined by guideline criteria such as those outlined in the 2015 Global Strategy for Asthma Management and Prevention [3], or by a set of criteria predefined in the included studies. The diagnosis of asthma was confirmed by a physician before the time of enrolment. Participants had to have taken a stable dose of inhaled corticosteroids for a minimum of two weeks before enrolment. Studies using oral corticosteroids were excluded.

Types of interventions

We included studies that compared continuing a stable daily maintenance dose versus increasing the daily dose of inhaled corticosteroids as part of an asthma exacerbation action plan. Active or placebo step-up therapy was to be increased shortly after the onset of symptoms signalling the beginning of an exacerbation. Other co-interventions such as long-acting beta agonists, leukotriene modifiers and other asthma medications were permitted, provided that the dose remained unchanged throughout the study. The only exception to this was the allowance of increased short-acting beta agonist use during exacerbations. Specifically, inhaled short-acting beta agonists and short courses of systemic corticosteroids were allowed as rescue medications.

Outcome measures

The critical and important outcomes in this review include all core outcomes for asthma exacerbations [16]. All were measured at longest follow up.

Critical outcomes

- Treatment failure - need for rescue systemic corticosteroids* in all randomised participants (intention-to-treat (ITT) analysis).
- Treatment failure - need for rescue systemic corticosteroids* in participants using the study inhaler (per protocol analysis)
- All (serious** and non-serious) adverse events

*oral, intramuscular or intravenous. The outcome definition for treatment failure involves participants being withdrawn from use of the study inhaler and started on rescue oral corticosteroids if they failed to respond adequately to an increase in inhaled corticosteroid dose, or if their peak expiratory flow rate dropped to below a predefined safety cut-off (usually 60%). Treatment failure was defined by deterioration or lack of improvement in pulmonary function or symptoms, or both. Rescue oral corticosteroids were participant-initiated if peak expiratory flow rate fell below a predefined threshold of 60% at any point during the treatment period, or after discussion with a study physician based on symptom frequency and peak expiratory flow rate measurements.

**Serious adverse events were defined as fatality, need for hospitalisation, prolongation of hospitalisation, disability and study withdrawal due to the adverse event. We noted in the analysis whether definitions used within these studies differed.

Important outcomes

- Unscheduled physician visits
- Unscheduled acute care or emergency department visits or need for hospital admission
- Duration of exacerbation as defined by: recovery of lung function; recovery of symptoms; or beta-2 agonist use back to baseline.

Search methods for identification of studies

All search methods and search strategies are presented in Supplementary material 1. This update includes searches up to 20 December 2021.

Electronic searches

Trials were identified from the Cochrane Airways Group Specialised Register (CAGR), which includes the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, handsearching of respiratory journals and meeting abstracts, and Clinicaltrials.gov.

We updated additional searches of the World Health Organization (WHO) ICTRP search portal for ongoing and unpublished trials. We searched all databases from their inception to the present, with no restriction on language of publication.

Searching other resources

We updated additional searches of trial registries and grey literature databases to identify articles that might not have appeared in the main electronic database searches (see Supplementary material 1). We also checked reference lists of retrieved articles and reviews and asked field experts if they knew of any relevant ongoing or unpublished trials.

Data collection and analysis

Selection of studies

We used 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 been labelled as an RCT or as Not an RCT; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs, and if appropriate, Cochrane Crowd – Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. More information about Screen4Me and the evaluations is available [17, 18, 19, 20].

Two review authors (EF and KK) independently screened titles and abstracts identified in the search using Covidence [15]. We retrieved full-text study reports for all references coded as 'include' by either review author. The same two review authors independently screened the full-text studies and recorded reasons for exclusion for excluded studies. We resolved disagreements through discussion or, if required, by consulting one of the clinical authors (BSQ or CL).

Data extraction and management

For this update, we replicated the previous data collection form for study characteristics and outcome data in Covidence [15], which had been piloted previously. Two review authors (EF and KK) extracted study data. Raw extracted study data is available via Figshare [21].

We resolved disagreements by reaching consensus and consulting with the clinical authors where required (BSQ and CL). One review author (EF) transferred study characteristics and risk of bias judgements into Review Manager (RevMan) [22], and two review authors (EF and KK) checked and transferred study data into the analyses. Cochrane Airways' editorial staff performed a statistics check to ensure data were entered correctly.

Risk of bias assessment in included studies

Two review authors (KK and EF) independently assessed risk of bias using RoB 2 [13, 14], August 2019 version, for all outcomes at latest follow-up listed in the Outcome measures section.

For all outcomes except treatment failure (need for rescue systemic corticosteroids in participants using the study inhaler), the effect of interest was the effect of assignment to the intervention (ITT). For treatment failure (need for rescue systemic corticosteroids in participants using the study inhaler), the effect of interest was the effect of adhering to the intervention (in this case, starting the study inhaler, a per-protocol effect). We resolved disagreements by discussion, and methodologists from the Cochrane Methods Support Unit reviewed judgements for accuracy and consistency. We assessed risk of bias for all RoB 2 domains and judged each domain as having 'high risk of bias', 'some concerns' or 'low risk of

bias' using the responses to the signalling questions and algorithms within the RoB 2 tool. The tool algorithm was used to reach an overall risk of bias for each outcome. We quoted evidence to support our judgements and if we disagreed with a judgement recommended by the algorithm, we included an explicit statement as to why. We managed our risk of bias assessments using the RoB 2 Excel tool (accessed January 2021) [23].

We used the guidance set out by the RoB 2 working group on cross-over trials and the tool extension to capture additional considerations associated with data from cross-over studies [24].

Measures of treatment effect

We analysed dichotomous data as odds ratios (ORs), and continuous data as mean differences (MDs) or standardised mean differences (SMDs). We entered data presented as a scale with a consistent direction of effect.

We undertook meta-analyses only when it was meaningful (i.e. when treatments, participants and the underlying clinical question were similar enough for pooling to make sense). For the treatment failure outcome, in some studies it was unclear whether the reported number of exacerbations was within the full randomised population or the subset who met criteria to start the study (both of which are critical outcomes in this review), and whether it was appropriate to include the same number of events in each analysis with a different denominator. We explicitly reported any assumptions that we made about the data in order to include study results in either treatment failure analysis.

We narratively described skewed data reported as medians and interquartile ranges.

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

Unit of analysis issues

We analysed data using participants with one or more events as the unit of analysis. For dichotomous outcomes, when we did not know whether the number of events applied to the entire population or only to those taking the study inhaler, we used the total number randomised per group as the denominator. We

performed sensitivity analyses by using the number of participants who used their study inhaler at least once as the denominator to test this assumption.

We pooled the results of parallel and cross-over studies when we were satisfied that data could be appropriately analysed to account for intercorrelation in cross-over studies. We obtained ORs from cross-over studies by comparing the number of participants who needed oral corticosteroids with increased dose (but not with placebo) versus those who needed oral corticosteroids while taking placebo (but not while taking an increased dose of inhaled corticosteroids).

Dealing with missing data

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

Reporting bias assessment

We were not able to pool more than 10 studies; therefore we did not create a funnel plot to explore possible small study and publication biases.

Synthesis methods

We completed all syntheses within RevMan [22]. We examined homogeneity of effect sizes between pooled studies, including with the I² statistic [25]. In the absence of heterogeneity, we used the fixed-effect model [26]; otherwise we applied summary estimates and reported the DerSimonian and Laird random-effects model [27]. Unless otherwise specified, we reported the fixed-effect model, as it is better equipped than the random-effects method to detect small effect sizes [28].

For dichotomous outcomes, we pooled parallel studies using Mantel-Haenszel ORs unless few events were reported, thus requiring Peto odds ratios (to avoid use of the continuity correction). For continuous outcomes, such as length of exacerbation, we calculated pooled statistics as MDs. All analyses included all eligible studies irrespective of risk of bias.

We grouped interventions for synthesis as follows:

Intervention characteristic	Intervention grouping	Rationale
Fold increase in baseline inhaled corticosteroids dose during exacerbation as part of an asthma exacerbation action plan	Double dose of inhaled corticosteroids More than double dose of inhaled corticosteroids	To understand if fold increase modifies the effect measure.

Investigation of heterogeneity and subgroup analysis

We planned the following a priori subgroup analyses of the critical outcomes to identify potential effect modifiers, irrespective of the presence or absence of heterogeneity.

- Age group (children < 15 years old versus adults ≥ 15 years old)

- Smoking status (smokers versus ex-smokers or never-smokers)
- Dose* of the stable daily maintenance dose of inhaled corticosteroids before increase (high versus medium versus low inhaled corticosteroids dose)

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- Achieved daily dose* of inhaled corticosteroids during exacerbation (high versus medium versus low inhaled corticosteroids dose)
- Time elapsed before initiation of treatment (> 48 hours versus < 48 hours)

*We classified the dose of inhaled corticosteroids dose according to Global Initiative for Asthma Guidelines [3] as follows.

- High dose:
 - Adults: > 1000 mcg/day of chlorofluorocarbon-propelled beclomethasone dipropionate (CFCBDP) dose or equivalent
 - Children: > 400 mcg/day equivalent CFC-BDP dose
- Moderate dose:
 - Adults: > 500 mcg to 1000 mcg/day CFC-BDP equivalent
 - Children: > 200 mcg to 400 mcg/day CFC-BDP equivalent
- Low dose:
 - Adults: 200 mcg to 500 mcg/day CFC-BDP equivalent
 - Children: 100 mcg to 200 mcg/day CFCBDP equivalent.

We converted fluticasone propionate to CFC beclomethasone dipropionate (CFC-BDP) equivalents by multiplying the ex-valve dose by two because its reported potency in asthmatic patients is two-fold relative to CFC-BDP [29]. Budesonide was converted to CFC-BDP equivalents by multiplying the ex-valve dose by 1.25, as reported in the Canadian Asthma Guidelines [30].

Equity-related assessment

We did not investigate equity-related characteristics in this review.

Sensitivity analysis

We planned the following sensitivity analyses for the critical outcome.

- Study design (removing cross-over studies)
- Methodological quality (removing studies with results we judged to be high risk of bias overall)

- Source of study funding (removing studies funded by pharmaceutical companies)

Certainty of the evidence assessment

We created a summary of findings table that included all outcomes listed in the [Outcome measures](#) section at longest follow-up.

We used the five GRADE considerations (overall risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to meta-analyses for prespecified outcomes. We used methods and recommendations described in Chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions to guide the application of GRADE methodology [31] through the GRADEpro GDT software [32].

Consumer involvement

Consumers were not involved in this review, although the review authors did use core outcome sets for the review's outcomes, which were developed with consumer involvement.

RESULTS

A complete record of all comparisons and analyses is available for this review in [Supplementary material 5](#) and a full data package is available in [Supplementary material 6](#).

Description of studies

Results of the search

The searches for this update covered March 2016 to 20 December 2021. Three database searches identified a total of 2212 records. [Figure 1](#) shows the screening process for this update with the number of studies brought forward from the previous version [11]. We identified one new study from the full-text articles assessed for eligibility (Jackson 2018 [33, 34]).

Figure 1. Study flow diagram

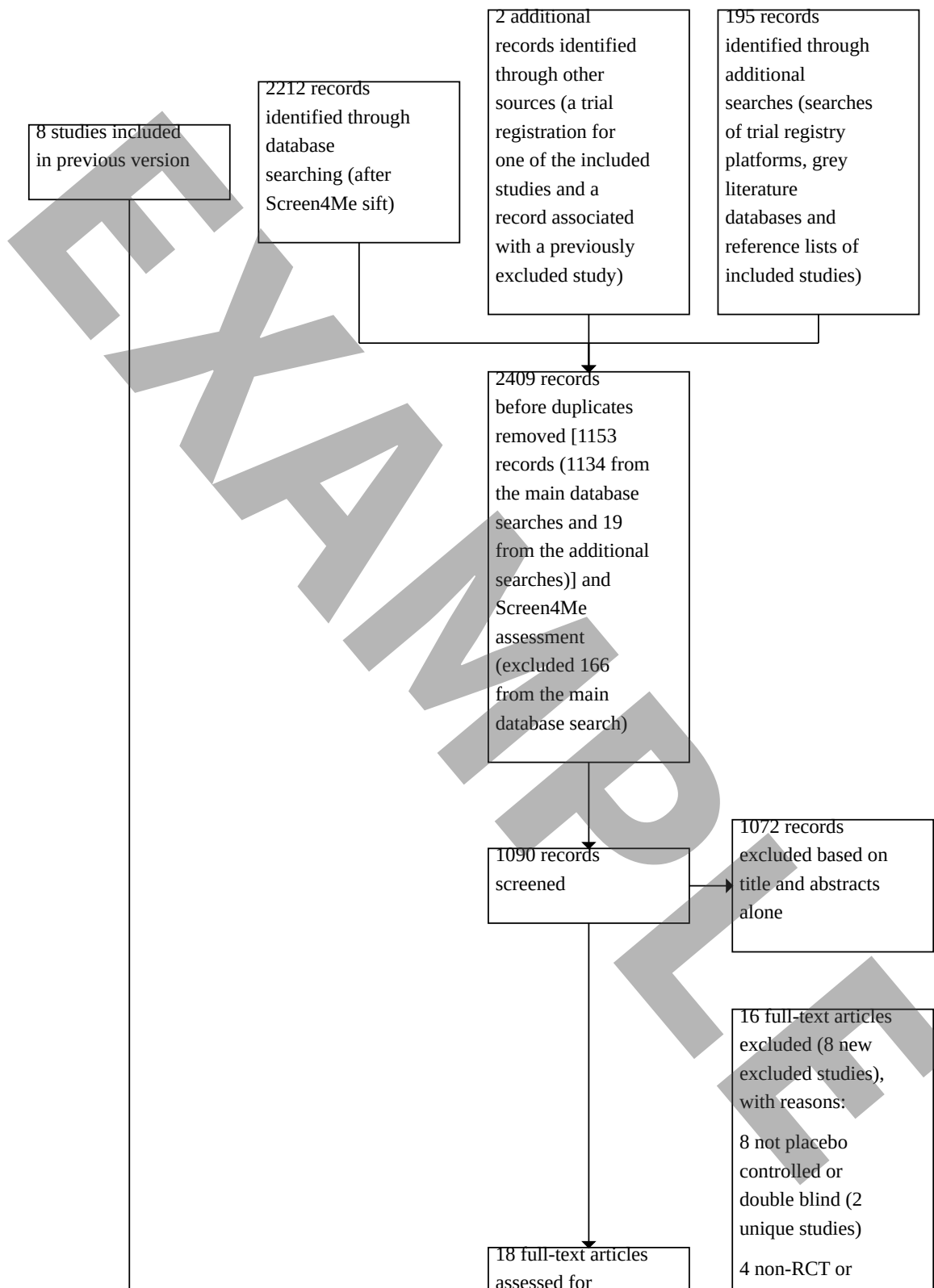
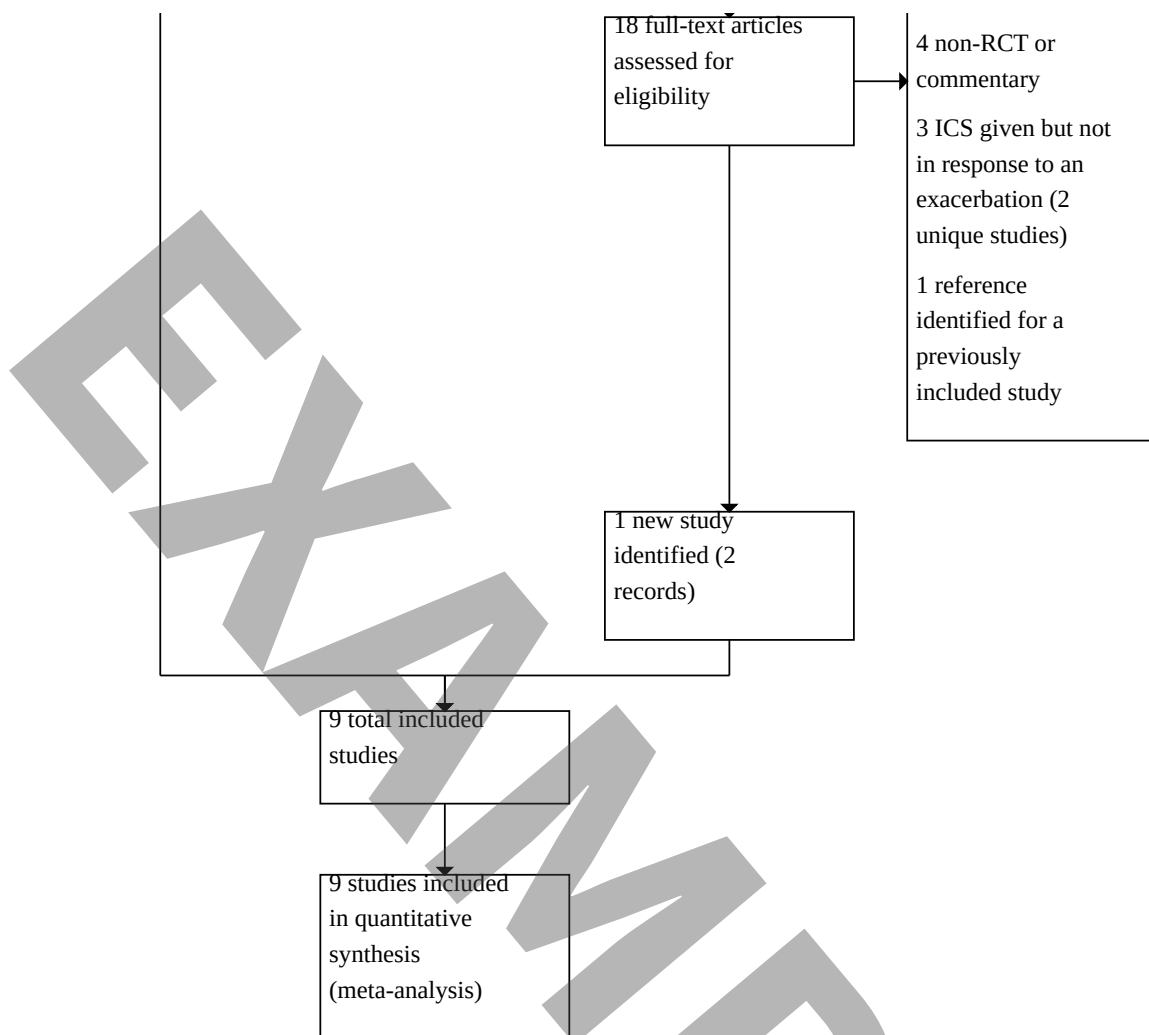


Figure 1. (Continued)



Included studies

The new study added to this review update included 254 participants (Jackson 2018), meaning a total of nine studies met the eligibility criteria with a total of 1923 participants. Of all randomised participants, 50.4% had an exacerbation that led to use of the study inhaler.

Table 1 is a summary of included studies and syntheses; key study characteristics important for interpreting the syntheses and full included studies details are available in Supplementary material 2

Characteristics of studies

Studies were conducted in Europe, North America, and Australasia and published between 1998 and 2018. Five studies evaluated adult populations (1247 participants; ≥ 15 years), and four studies evaluated child or adolescent populations (676 participants; < 15 years). Approximately 50% of randomised participants initiated the study inhaler (range 23% to 100%). The included studies reported treatment failure in a variety of ways, meaning we needed to make assumptions to allow us to combine data. All studies were

published as full-text papers except for Wainwright 2009 [35], for which study details and results were provided by the lead investigator.

Characteristics of participants

Details about the age range, gender, smoking status and asthma severity of participants in each study are shown in Supplementary material 2.

For the purpose of the subgroup analysis by age (children < 15 years versus adults ≥ 15 years), we classified four studies as having child populations (Garrett 1998 [36]; Jackson 2018; Martinez 2011 [37]; Wainwright 2009) and five studies as having adult populations (FitzGerald 2004 [38]; Foresi 2000 [39]; Harrison 2004 [40]; Osborne 2009 [41]; Rice-McDonald 2005 [42]). FitzGerald 2004 had a lower age limit of 13 years and we included it in within the adult subgroup because the age range was more consistent with the adult studies and the mean age of participants was 32 years. Similarly, Martinez 2011 included adolescents up to 18 years and we classified it as a child population because the age range was more consistent with the other child studies and the mean age was 11 years. Mean

participant age in the five adult studies ranged from 32 to 56 (median 46.5) years and mean participant range from the four paediatric studies ranged from 7.6 to 11 (median 8.1) years (we calculated a rough mean age of 7.6 from age-group categories reported for Wainwright 2009). Inclusion criteria for each study are in [Supplementary material 2](#).

Treatment format

During the original protocol development for this review it was not anticipated that this would be a complex intervention. However, as more studies have been added at each update, complexities in the designs have resulted in the creation of [Supplementary material 8](#), which highlights differences in treatment format for each study.

Outcome reporting and assumptions required for synthesis

[Table 1](#) shows which studies contributed results to which syntheses. For the treatment failure outcomes, we explicitly reported in [Supplementary material 2](#) any assumptions that we needed to make about the study results data in order to include them in either treatment failure analysis.

Where we needed to make assumptions to include studies in the review analyses, we also captured the potential for introducing missing data biases into the analysis within the risk of bias assessments for those results (see [Supplementary material 4](#)). This was most notable when studies reported the number of events (e.g. treatment failures) for the subset of people who had an exacerbation and started the study inhaler (or reported a number of events or percentage without stating the population), and we included those data with the denominator for the full population for treatment failure in the analysis of all randomised participants. Doing so assumes that those who did not start the study inhaler did not have the event of interest, and the potential for bias depends on the size of the subset as a proportion of the full population.

Excluded studies

We added eight new excluded studies in this update to the 39 excluded in previous versions, giving a total of 47 excluded studies. Reasons for exclusion are documented in [Supplementary material 3](#). Common reasons for exclusion across all versions of the review included the absence of a placebo control, recruitment of a population who were not taking maintenance inhaled corticosteroids, and a design that compared the relative effectiveness of two doses of inhaled corticosteroids as maintenance therapy rather than changing the dose in response to worsening symptoms. Two studies excluded in this update, one of which was a large and independently funded study (McKeever 2018 [43, 44, 45, 46, 47, 48]), assessed the research question of interest but in a pragmatic and unblinded design, which did not meet the eligibility criteria for the review.

No studies were classified as awaiting classification or ongoing.

Risk of bias in included studies

We have included risk of bias assessments and support for judgements across all RoB 2 domains for each outcome prespecified for risk of bias assessments in [Supplementary material 4](#). For the two cross-over trials (Garrett 1998; Rice-McDonald 2005), the cross-over trial specific risk of bias assessments and support for judgements are detailed in the overall risk of bias column. Full consensus responses to the signalling questions for each domain across all studies and results are available via Figshare [49].

In general, there was low risk of bias arising from the randomisation process from across the studies. Four studies had some concerns in only one of the RoB 2 domains but the overall reporting and conduct of these studies suggested they had followed rigorous procedures to minimise bias. Therefore, we overwrote the RoB 2 tool algorithm for these studies and judged the overall risk of bias to be low (Harrison 2004; Martinez 2011; Osborne 2009; Jackson 2018; in [Supplementary material 4](#)).

There was a notable difference between the risk of bias assessments for treatment failure in the different populations (all randomised participants versus those starting the inhaler). Half of the studies that contributed results to treatment failure in all randomised participants had an overall low risk of bias and half had some concerns or high risk of bias. Whereas, for studies that contributed results to treatment failure in those who started the inhaler, all but one study was at high risk of bias overall. Domains that contributed to high risk of bias were deviations from intended interventions or missing outcome data, mainly as it was unclear whether the reported counts related to the full randomised population or only those who took their study inhaler; the events were similar in number or fewer than the number who dropped out, with reasons for dropping out potentially relating to the participants' health. Similar reasons were seen for the risk of bias for results contributing to adverse events, of which three studies had a high risk and one had some concerns.

Synthesis of results

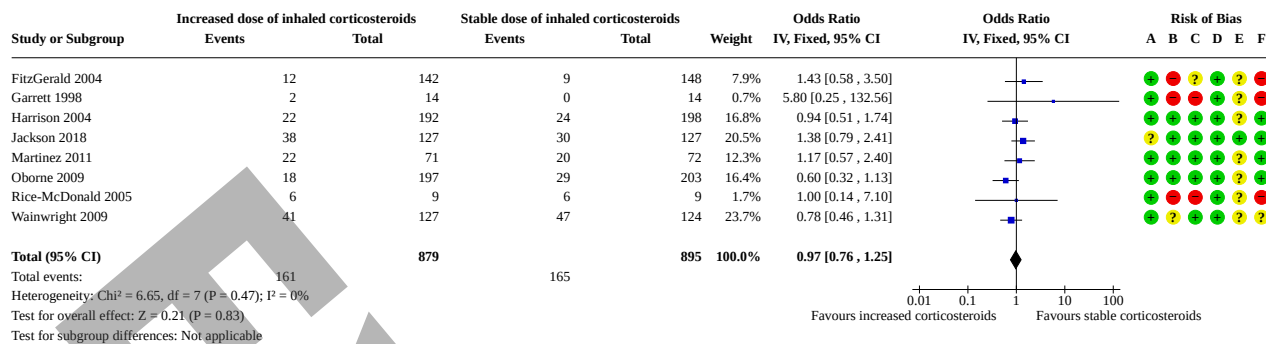
Absolute and relative effects for all critical and important outcomes are summarised with their GRADE ratings signifying confidence in the effect estimates in [Summary of findings 1](#).

Critical outcomes

Treatment failure (need for systemic corticosteroids) in all randomised participants: intention-to-treat analysis

People randomised to increase their inhaled corticosteroid dose at the first signs of an exacerbation had similar odds of requiring rescue oral corticosteroids to those randomised to take a placebo inhaler (OR 0.97, 95% CI 0.76 to 1.25; I² = 0%; 8 studies, 1774 participants; [Figure 2](#)). Approximately 50% of randomised participants actually required use of the study inhaler (mean 50.4%, range 23% to 100%).

Figure 2. Forest plot for the outcome treatment failure (need for systemic corticosteroids) in all randomised participants



Risk of bias legend
 (A) Bias arising from the randomization process
 (B) Bias due to deviations from intended interventions
 (C) Bias due to missing outcome data
 (D) Bias in measurement of the outcome
 (E) Bias in selection of the reported result
 (F) Overall bias

We had moderate confidence in the result due to concerns around risk of bias and the assumptions we had to make to include study data in the intention-to-treat (ITT) and treated population analyses (see [Supplementary material 9](#)). While we did not prespecify bounds for concluding no difference or assessing imprecision, the point estimate and width of the confidence intervals suggest that there is unlikely to be a clinically important effect of increasing inhaled corticosteroid dose to avoid the need for oral steroids. In absolute terms, 184 people out of 1000 needed oral corticosteroids in the control group over 46 weeks, compared with 180 (95% CI 147 to 220) out of 1000 for those randomised to increase their inhaled corticosteroid dose in the event of an exacerbation.

There were sufficient data to investigate five of the six expected effect modifiers with subgroup analyses. Results did not suggest a visible or statistical difference between the subgroups investigated, but the observational nature of subgroup analysis and the small number of studies in each subgroup means the possibility of important differences cannot be ruled out (see [Supplementary material 5](#) for full analyses relating to subgroups).

- Adult versus paediatric study populations (test for subgroup differences: Chi² = 0.71, df = 1, P = 0.40, I² = 0%)
- Initiation of the study inhaler within 48 hours versus after 48 hours (test for subgroup differences: Chi² = 0.43, df = 1, P = 0.51, I² = 0%)
- Low versus medium versus high maintenance doses of inhaled corticosteroids (test for subgroup differences: Chi² = 2.92, df = 2, P = 0.23, I² = 31.5%)
- Low versus high exacerbation doses of inhaled corticosteroids (test for subgroup differences: Chi² = 1.10, df = 1 (P = 0.30), I² = 8.7%)
- Doubling versus larger dose increases (test for subgroup differences: Chi² = 0.01, df = 1, P = 0.91, I² = 0%)

We could not include Garrett 1998 in the maintenance or exacerbation inhaled corticosteroid dose subgroup analyses

because of the large dose range, which included no details about average doses on which to base a categorisation. We could not examine the impact of smoking status on the odds of requiring oral corticosteroids during an exacerbation because all studies recruited non-smokers or ex-smokers.

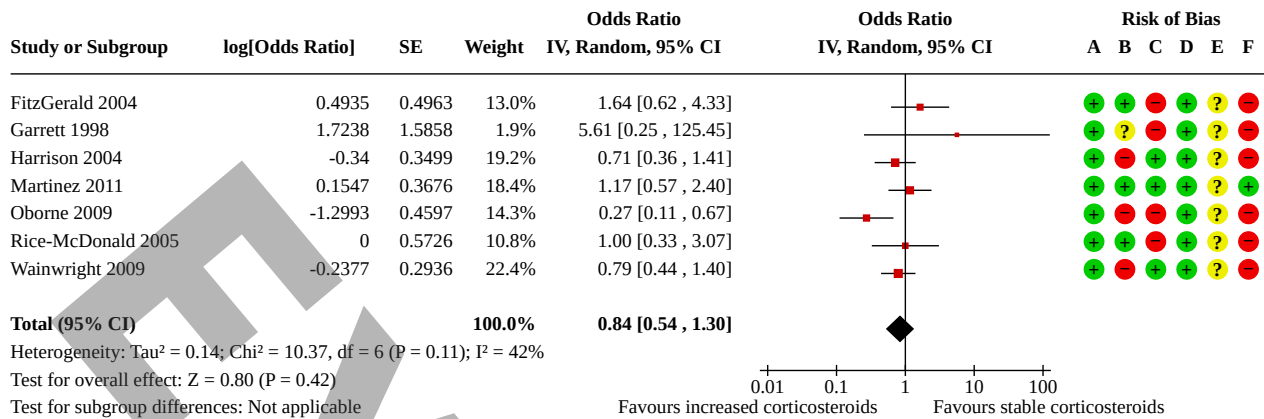
There was overlap in the studies removed in the planned sensitivity analysis and results should be considered exploratory. The results showed minimal impacts on the synthesised result for the critical outcome (see [Supplementary material 5](#) for full sensitivity analyses).

- Removing the two cross-over studies (OR 0.96, 95% CI 0.74 to 1.24; I² = 7%)
- Removing the three studies at overall high risk of bias (OR 0.93, 95% CI 0.71 to 1.21; I² = 13%)
- Removing the two commercially funded studies (OR 0.93, 95% CI 0.71 to 1.21; I² = 0%)

Treatment failure (need for systemic corticosteroids): treated population analysis

Results within the treated population to assess the effect of increasing inhaled corticosteroid dose in participants who needed to initiate the study inhaler remain unchanged from the previous version of the review, because the new study (Jackson 2018), only reported results for the full randomised population. The analysis is based on 766 people who had exacerbations and met the study criteria to initiate the study inhaler, rather than all 1774 full randomised sample. The point estimate was more in favour of increased inhaled corticosteroid dose than the primary ITT analysis, but does not suggest that participants randomised to increase their inhaled corticosteroids dose have lower odds of requiring oral corticosteroids than those assigned to placebo (OR 0.84, 95% CI 0.54 to 1.30; I² = 42%; 7 studies, 766 participants; random-effects model used; [Figure 3](#)).

Figure 3. Forest plot for the outcome treatment failure (need for systemic corticosteroids) in participants starting their study inhaler



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions
- (C) Bias due to missing outcome data
- (D) Bias in measurement of the outcome
- (E) Bias in selection of the reported result
- (F) Overall bias

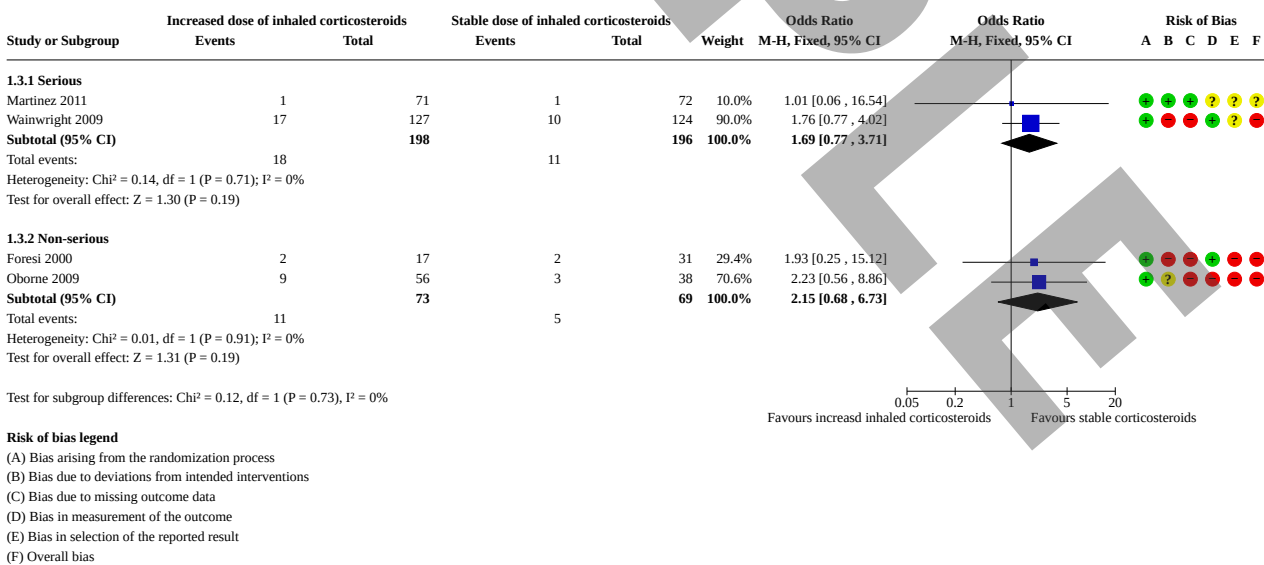
In two studies, all randomised participants took their study inhaler, so the data were the same as those entered for the critical outcome. We had very low confidence in the result because of inconsistency between study results, imprecision in the pooled effect, and very serious risk of bias (see [Supplementary material 9](#)).

All adverse events

We analysed serious adverse events and non-serious adverse events separately due to the way they were reported in the included

studies, with two pairs of different studies in each analysis (no new data since the previous version of the review). The point estimates both lay in favour of keeping inhaled corticosteroids stable, but imprecision reduced our confidence in the effect estimates (serious adverse events OR 1.69, 95% CI 0.77 to 3.71; I² = 0%; 2 studies, 394 participants; non-serious adverse events OR 2.15, 95% CI 0.68 to 6.73; I² = 0%; 2 studies, 142 participants [Figure 4](#)).

Figure 4. Forest plot for the outcome serious and non-serious adverse events



- Risk of bias legend**
- (A) Bias arising from the randomization process
 - (B) Bias due to deviations from intended interventions
 - (C) Bias due to missing outcome data
 - (D) Bias in measurement of the outcome
 - (E) Bias in selection of the reported result
 - (F) Overall bias

We had very low confidence in either result due to imprecision and risk of bias, primarily arising from missing data and additionally from measurement of the outcome and selection of the reported result for non-serious adverse events (see [Supplementary material 9](#)).

Serious adverse events in Martinez 2011 included bronchitis in the increased dose group and viral meningitis in the stable daily dose group. Wainwright 2009 reported six occurrences of upper respiratory tract infection/otitis media/croup in the increased inhaled corticosteroids group and between low numbers of the following in one or both groups, for which no formal analyses have been conducted: ear/nose/throat surgery, fracture and orthopaedic events, chest infection/pneumonia, and death (one in the double-dose group). Three studies reporting lists of specific non-serious side effects generally showed low occurrence (one or two people

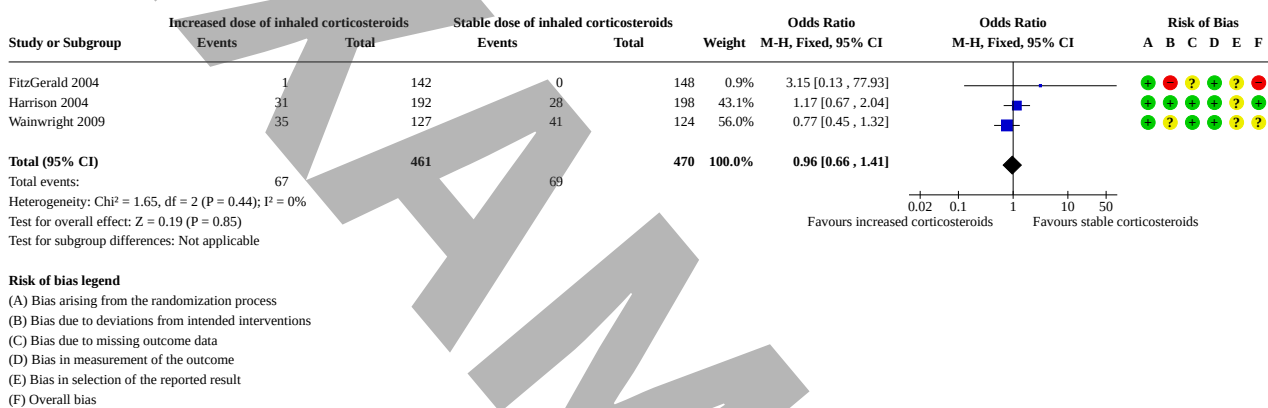
in either group (Foresi 2000; Osborne 2009; Rice-McDonald 2005), and Garrett 1998 and Harrison 2004 provided minimal information regarding adverse events.

Important outcomes

Unscheduled physician visits

The pooled effect of three parallel-group studies that could be included in the analysis was very imprecise (OR 0.96, 95% CI 0.66 to 1.41; I² = 0%; 3 studies, 931 participants; [Figure 5](#); unchanged from previous version of the review). Harrison 2004 and Wainwright 2009 reported unscheduled visits only for people who took their study inhaler, but we used the total number randomised as the denominator. A post hoc sensitivity analysis using only those taking the study inhaler as the denominator for these two studies, did not change the conclusions (OR 0.89, 95% CI 0.59 to 1.35).

Figure 5. Forest plot for the outcome unscheduled physician visits



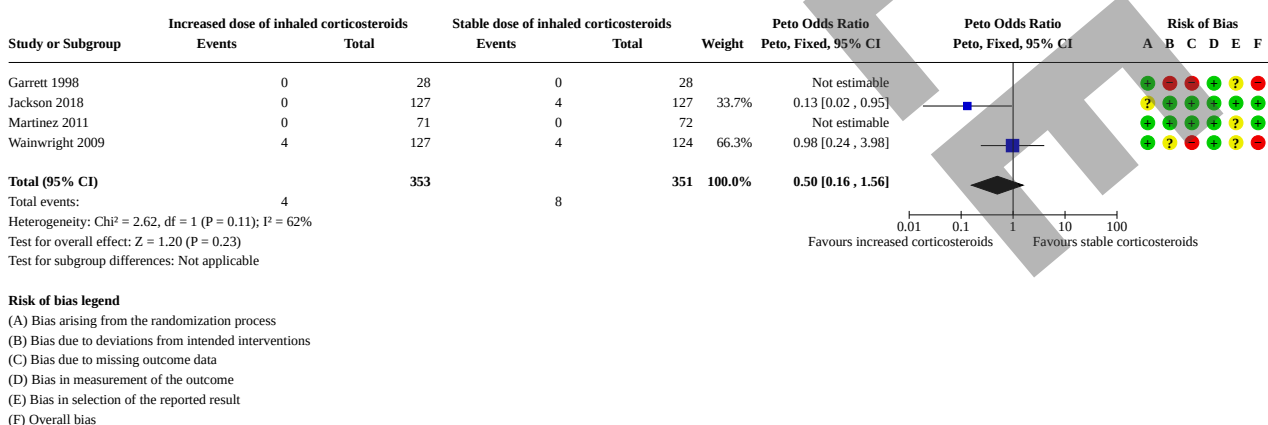
The width of the confidence intervals makes it very difficult to determine where the true effect may lie so our confidence in the effect estimate is low.

Unscheduled acute care and emergency department visits or need for hospital admission

The pooled effect of three studies that could be included in the analysis was very imprecise because only one study observed any

events (Peto OR 0.50, 95% CI 0.16 to 1.56; 4 studies, 704 participants; [Figure 6](#)). Conclusions were unchanged when the number taking the study inhaler instead of the number randomised was used as the denominator (Peto OR 0.52, 95% CI 0.17 to 1.65; 4 studies, 505 participants).

Figure 6. Forest plot for the outcome unscheduled acute care, emergency department visit or hospital admission



We had very low confidence in the effect estimate due to very serious imprecision and risk of bias (see [Supplementary material 9](#)).

Duration of exacerbation

We made no changes to the analyses of duration of exacerbation from the previous version of the review. Although three studies reported the outcome defined by the time required for peak expiratory flow rate to return to baseline values (Garrett 1998; Harrison 2004; Osborne 2009), group mean and standard deviation

values were only available for Harrison 2004, which did not suggest a difference between stable and increased inhaled corticosteroids (Figure 7; Figure 8). Mean time to symptom recovery in the placebo group was 6.1 days and mean time to lung function recovery was 7 days. In those who took an increased dose of inhaled corticosteroids, time to recovery was 0.7 days longer (95% CI 1.06 shorter to 2.46 longer) and 0.2 days shorter (95% CI 1.88 shorter to 1.47 longer), respectively.

Figure 7. Forest plot for the outcome duration of exacerbation (days to symptom recovery)

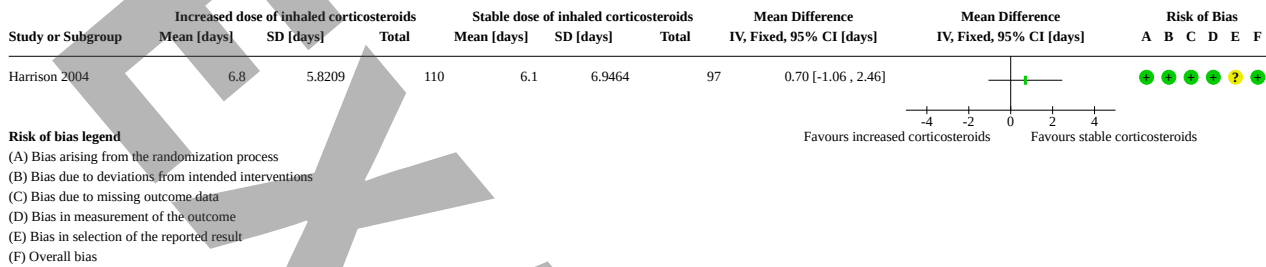
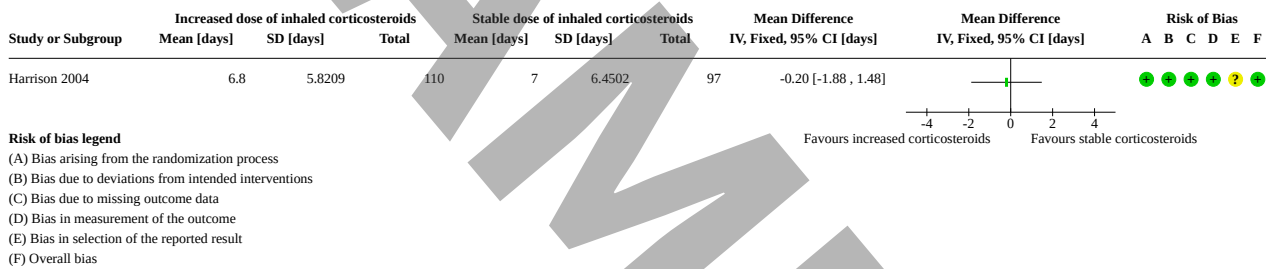


Figure 8. Forest plot for the outcome duration of exacerbation (days to lung function recovery)



We had low confidence in the estimates due to risk of bias and imprecision (see [Supplementary material 9](#)).

DISCUSSION

Summary of main results

Evidence suggests that adults and children with mild to moderate asthma are unlikely to see a clinically meaningful reduction in the need for oral steroids from increasing a patient's inhaled corticosteroid dose at the first sign of an exacerbation. Other clinically important benefits and potential harms cannot be ruled out due to wide confidence intervals, risk of bias in the studies, and assumptions made for synthesis when combining data.

This review includes nine studies with a total of 1923 participants. With the addition of one study in this review update, there is increased confidence in the bottom-line finding for treatment failure in all randomised participants, but the new study sheds little additional light on the infrequent adverse events and important outcomes around hospital attendance and resource use, which likely reflects the mild-to-moderate asthma of the recruited populations. Furthermore, the reliance on aggregate data from a relatively small number of moderately sized, heterogeneous studies means that there is little information for investigation of the cost-benefit profiles of the strategy for populations at different

baseline doses, or different dose increases against other strategies, and their interplay with clinical characteristics.

Limitations of the evidence included in the review

A full summary of the considerations that led to downgrading or upgrading the certainty of the evidence in the implementation of GRADE is in [Supplementary material 9](#). Thresholds used for downgrade decisions are explicitly stated (e.g. for concluding no difference).

To our knowledge, this is the only systematic review and meta-analysis in the literature examining the safety and effectiveness of increasing versus maintaining the same inhaled corticosteroid dose at the onset of an asthma exacerbation as part of a patient-initiated action plan. The study populations included in this review were those with mild to moderate asthma, and therefore, the results may not be applicable to those with severe asthma. The criteria for action plan activation were based on a combination of peak expiratory flow rate worsening, increase in asthma symptoms, and an increase in rescue bronchodilator use, which reflect current clinical practice.

The primary objective of some studies was to measure the need for oral steroids in those who started the study inhaler, which ignores potential differences in exacerbation frequency and

intervention application between groups, and blurs a lack of need with other reasons for failing to initiate the study inhaler, such as suboptimal adherence or understanding. More recent studies follow the intention-to-treat approach to measure the effect of being allocated to a stable or increased inhaled corticosteroid action strategy regardless of how frequently or accurately it was enacted, assuming any differences reflect those that would occur in practice. Though the intention-to-treat approach is more methodologically reliable, both angles are likely to be of interest to decision makers and our confidence is reflected in the risk of bias assessments and GRADE ratings.

The overall lack of benefit from an increased inhaled dose strategy on the treatment failure outcomes may be due to several reasons. First, most study participants were on maintenance inhaled corticosteroid which is an effective method of preventing exacerbations and, specifically, for reducing the need for rescue oral corticosteroids. In several of the included studies, the dose of maintenance inhaled corticosteroid was in a high range. Therefore, further increasing the inhaled corticosteroid dose at the onset of a respiratory exacerbation may have little benefit given the shape of the dose-response curve [50]. In addition, although self-reported compliance with the action plan protocol and study inhaler was high, actual compliance was not monitored or measured objectively. Among the studies, there were minor differences in the timing of action plan activation after symptom onset or peak expiratory flow rate worsening, ranging from immediate start to 48 hours after. This detail is important to note as a delay in initiating increased inhaled corticosteroid may also affect clinical outcomes.

Limitations of the review processes

A number of complexities have arisen during the life cycle of this review due to changes in practice and methodology, which have required deviations from the original protocol published in 2009 [12] and post hoc decision-making by the review authors. The most notable evolution within the review, which has the potential to introduce bias, is the approach to defining the critical outcomes of treatment failure and the assumptions that can be reasonably made to account for variations in study outcome reporting. The nature of differences in how study investigators defined their outcome population (intention-to-treat or treated population) and how they dealt with people who did not initiate the study inhaler were not fully anticipated. Unclear reporting and study definitions that did not match the preferred intention-to-treat population for the meta-analysis meant that we needed to make assumptions in order to include study data, and we have made these explicit throughout the methods, results and in supplementary files to allow our choices to be interrogated, understood and reanalysed as necessary.

We also deviated from the study protocol in order to increase efficiency and bring the review up to date with current methods, including the type of software used for study processes, and elaborating risk of bias methods for the revised Cochrane risk of bias tool for randomised controlled trials [13, 14]. Data assumptions and transformations are all provided in supplementary materials and supplementary files.

Agreements and disagreements with other studies or reviews

For this review update, the overall study findings and conclusions were consistent with those of our prior review. There were two pragmatic studies that we excluded with findings that are in disagreement with our review but provide insightful perspectives.

In a recent, non-blinded, randomised trial involving adults and adolescents with asthma, McKeever 2018 compared a self-management plan that included quadrupling versus not quadrupling the dose of inhaled glucocorticoids. The non-blinded nature of the intervention was the reason for exclusion from this review. The adjusted hazard ratio for the time to a first severe asthma exacerbation, defined as treatment with systemic glucocorticoids or an unscheduled healthcare consultation for asthma, over a 12-month period was 0.81 (95% CI 0.71 to 0.92, $P = 0.002$). Furthermore, the percentage of participants who used systemic glucocorticoids was lower in the quadrupling group than in the nonquadrupling group (33% versus 40%), with a mean number of courses of 0.50 versus 0.61 (incidence rate ratio, 0.82; 95% CI 0.70 to 0.96). Among those who reported activation of the self-management plan, 50% of those in the quadrupling group and 42% of those in the nonquadrupling group were judged to have good adherence. In this pragmatic study, 80% of the participant recruitment was in primary care. Approximately 50% of the participants included in the trial had an exacerbation within a year, which may suggest more poorly controlled baseline. These factors may account for the observed benefit of quadrupling inhaled glucocorticoids in this study.

Cardet and colleagues published a pilot study to determine the feasibility of a pragmatic trial testing the PatientActivated Reliever-Triggered ICS (PARTICS) strategy of using inhaled corticosteroids concomitantly with rescue inhalers [51]. The study population included mostly female (age > 40 years), African-American and Hispanic participants who had uncontrolled asthma (mean Asthma Control Test score < 20) of varying severity (mild, moderate, severe). Although participant recruitment was feasible in the allotted 12-week time frame, key findings included low response rates (61% to 70%) and self-reported adherence (62% to 88%), which led to the need for modifications to the full study protocol. These pragmatic clinical trials likely better reflect the real-world setting, which can inform our interpretation of the results in efficacy trials.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from double-blind trials of adults and children with mild to moderate asthma suggests that there is unlikely to be a clinically meaningful reduction in the need for oral steroids from increasing a patient's inhaled corticosteroid dose at the first sign of an exacerbation. Other clinically important benefits and potential harms of increased doses of inhaled corticosteroids compared with keeping the dose stable cannot be ruled out due to wide confidence intervals, risk of bias in the studies, and assumptions that we had to make for synthesis. Included studies conducted between 1998 and 2018 reflect evolving clinical practice and study methods, and the data did not support thorough investigation of effect modifiers such as baseline dose, fold increase, asthma severity and timing. The review does not include recent evidence from pragmatic, unblinded

studies that suggest a benefit of larger dose increases in those with poorly controlled asthma.

Implications for research

A new systematic review protocol may be warranted to look at the differences between the blinded and unblinded evidence using robust methods for assessing risk of bias, in order to present and critique the full evidence base for decision makers. Access to individual patient data in one or more of the larger, more recent trials may shed light on effect modifiers that are difficult to investigate with aggregate data across a small set of heterogeneous studies. Effectiveness in patients with lower baseline inhaled corticosteroid dose and higher fold increases may be a reasonable focus in light of recent findings from pragmatic studies. Additional randomised controlled trials of a similar size in comparable populations are unlikely to add much certainty to what is already known from this review given the extent of existing variation between studies and the low frequency of important resource-use outcomes in the population of interest. It remains a priority for study investigators to report core outcomes consistently and transparently with clear descriptions of the population on which the analysis was conducted, and to provide access to raw and adjusted data to facilitate reanalysis and synthesis. Clear and structured descriptions of complex intervention components are also key in research to support synthesis for implementation.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: N/A.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Risk of bias

Supplementary material 5 Analyses

Supplementary material 6 Data package

Supplementary material 7 Differences between the protocol and previous versions

Supplementary material 8 Intervention treatment format in included studies

Supplementary material 9 GRADEing the certainty of the evidence

ADDITIONAL INFORMATION

Acknowledgements

Cochrane Airways supported the authors in the development of this review. We are grateful to all authors who developed the protocol for this review [12] and contributed to previous review versions in 2010 [10] and 2016 [11]. We are very grateful to the study authors Vernon Chinchilli, Fernando Martinez, Claire Wainwright, Tim Harrison and Janet Osborne, who kindly responded to requests for additional information for the previous version and this review update.

The following people conducted the editorial process for this review via Cochrane Airways: Sally Spencer (Co-ordinating Editor); Iain Crossingham (Contact Editor); Rebecca Fortescue (Co-ordinating Editor), including statistical data checks pre-submission; Emma Dennett (Deputy Co-ordinating Editor); Emma Jackson (Managing Editor); Elizabeth Stovold (Information Specialist), including designing the search strategy, running the searches, and editing the search methods section. We also thank Cochrane's Methods Support Unit for checking our risk of bias assessments pre-submission.

Contributions of authors

KK: co-lead for the 2016 and 2021 updates (sift and study selection, data extraction, analysis, risk of bias and GRADE assessment, write-up). EF: co-lead for the 2021 update (sift and study selection, data extraction, analysis, risk of bias and GRADE assessment, write-up). CL: critical appraisal of 2021 update (clinical input for inclusion decisions, contributing to write up, reviewing manuscript). BSQ: study assessment, data extraction and write-up of first review version (2010), critical appraisal of 2016 and 2021 updates (clinical input for inclusion decisions, contributing to write up, reviewing manuscript).

Some authors involved in previous published versions of this review are no longer included on the author byline. Some of the content retained in this review reflects their contributions. Francine Ducharme helped develop the original protocol and contributed in the interpretation, write-up and sign-off of the 2010 and 2016 reviews; Michael Quinn co-led the 2016 update including sift and study selection, data extraction, analysis, risk of bias assessment and write-up; Mark FitzGerald, Catherine Lemièrre and Neal Shahidi were all authors for the 2010 version and their contributions are described in previous versions.

Declarations of interest

KK: former employee of the Cochrane Central Executive Team (2020-2021), during which time most of the work for the update was completed, and former employee of the Cochrane Airways editorial team (2012 to 2016). No commercial or non-commercial conflicts of interest relevant to this review. EF: employee of the Cochrane Central Executive Team. No commercial or non-commercial conflicts of interest relevant to this review. BQ: no commercial or non-commercial conflicts of interest relevant to this review. CL: no commercial or non-commercial conflicts of interest relevant to this review.

Sources of support

Internal sources

- No internal sources of support received., Other
- Not applicable

External sources

- National Institute for Health and Care Research, UK

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Registration and protocol

Protocol (2009) [12]

Original review (2010) [10]

Review update (2014) [11]

Data, code and other materials

As part of the published Cochrane Review, the following are made available for download for users of the Cochrane Library: full search strategies for each database; full citations of each unique

What's new

report for all studies included, ongoing or awaiting classification, or excluded at the full-text screen, in the final review; study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows. Appropriate permissions have been obtained for such use. Analyses and data management were conducted within Cochrane's authoring tool, Review Manager Web, using the inbuilt computation methods. Template data extraction forms from Covidence are available from the authors on reasonable request.

Date	Event	Description
20 December 2021	New citation required and conclusions have changed	One new study added, methods updated to use the revised risk of bias tool for randomised controlled trials, including reapplication of GRADE for all outcomes. Though there is increased confidence in the bottom-line finding for treatment failure in all randomised participants, the new study sheds little additional light on the infrequent adverse events and important outcomes around hospital attendance and resource use, which likely reflects the mild to moderate asthma severity of the recruited populations.
20 December 2021	New search has been performed	New literature search run.

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EXAMPLE

ADDITIONAL TABLES

Table 1. Overview of included studies and syntheses

Study ID (country) ^a	Study design	N randomised ^b	N (%) who took study inhaler at first signs of exacerbation	Population (age range/ % male)	Asthma severity at baseline (ICS dose at baseline)	Increased ICS dose at first signs of exacerbation ^c	Outcome with available data (synthesis method)
FitzGerald 2004 (Canada)	6-month parallel, DB, PC	290	98 (34)	13+ / 28	NR (635 mcg/d, mean)	Doubled	Treatment failure ITT (MA); treatment failure per protocol (MA); physician visits (MA)
Foresi 2000 (Italy)	6-month parallel, DB, PC	142	36 (25)	18-65 / 47	Moderate (500-1000 mcg/d, range)	Quadrupled	Adverse events (MA)
Garrett 1998 (New Zealand)	6-month cross-over, DB, PC	28	18 (64)	6-14 / 68	Mild to moderate (not exceeding 800 mcg/d, range)	Doubled	Treatment failure ITT (MA); treatment failure per protocol (MA); hospital admission (MA)
Harrison 2004 (UK)	1-year parallel, DB, PC	390	207 (53)	16+ / 33	NR (710 mcg/d, mean)	Doubled	Treatment failure ITT (MA); treatment failure per protocol (MA); physician visits (MA); duration (MA)
Jackson 2018 (USA)	48-week parallel, DB	254	168 (66)	5-11 / 64	Mild to moderate (NR)	Quintupled	Treatment failure ITT (MA); hospital admission (MA)
Martinez 2011 (USA)	44-week parallel, DB, PC	143	143 (100)	6-18 / 57	Mild ($\leq 160 \mu\text{g}$ daily equivalent)	Double	Treatment failure ITT (MA); treatment failure per protocol (MA); adverse events (MA); hospital admission (MA)
Oborne 2009 (UK)	1-year parallel, DB, PC	403	94 (23)	16+ / 32	NR (520 mcg, mean)	Doubled	Treatment failure ITT (MA); treatment failure per protocol (MA); adverse events (MA)
Rice-McDonald 2005 (Australia)	Cross-over until exacerbation in each phase	22	18 (82)	18+ / 41	Mild and moderate (NR)	Doubled	Treatment failure ITT (MA); treatment failure per protocol (MA)
Wainwright 2009	1-year parallel, PC	251	187 (75)	3-14 / 60	NR (minimum 125 mcg fluticasone/d; 27% on 500 mcg/	Doubled	Treatment failure ITT (MA); treatment failure per protocol (MA); adverse events

Table 1. Overview of included studies and syntheses (Continued)
(Australia)

day ICS and 9% >
500mcg/day ICS)

(MA); physician visits (MA); hospital ad-
mission (MA)

DB: double-blind; **ED:** emergency department; **ICS:** inhaled corticosteroids; **ID:** identifier; **ITT:** intention to treat; **MA:** meta-analysis, **N:** number, **NR:** not reported, **PC:** placebo-controlled, **UK:** United Kingdom; **USA:** United States of America.

^aSee [Supplementary material 2](#) for full study details, including study inclusion, exclusion criteria and full baseline characteristics.

^bThe number randomised to the groups relevant to this review.

^cFull intervention details for each study available in [Supplementary material 8](#).

EXAMPLE

INDEX TERMS**Medical Subject Headings (MeSH)**

*3-Iodobenzylguanidine; Neuroblastoma [*diagnostic imaging] [pathology] [secondary]; *Positron-Emission Tomography; Sensitivity and Specificity; *Tomography, Emission-Computed, Single-Photon

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Infant, Newborn

EXAMPLE