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[Intervention Review]

Patient- and parent-initiated oral steroids for asthma exacerbations

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ABSTRACT

Background

Asthma is a chronic inflammatory disease of the airways affecting an estimated 334 million people worldwide. During severe exacerbations, patients may need to attend a medical centre or hospital emergency department for treatment with systemic corticosteroids, which can be administered intravenously or orally. Some people with asthma are prescribed oral corticosteroids (OCS) for self-administration (i.e. patient-initiated) or to administer to their child with asthma (i.e. parent-initiated), in the event of an exacerbation. This approach to treatment is becoming increasingly common.

Objectives

To evaluate the effectiveness and safety of patient- or parent-initiated oral steroids for adults and children with asthma exacerbations.

Search methods

We identified trials from Cochrane Airways' Specialised Register (CASR) and also conducted a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch). We searched CASR from its inception to 18 May 2016 and trial registries from their inception to 24 August 2016; we imposed no restriction on language of publication.

Selection criteria

We looked for randomised controlled trials (RCTs), reported as full-text, those published as abstract only, and unpublished data; we excluded cross-over trials.

We looked for studies where adults (aged 18 years or older) or children of school age (aged 5 years or older) with asthma were randomised to receive: (a) any patient-/parent-initiated OCS or (b) placebo, normal care, alternative active treatment, or an identical personalised asthma action plan without the patient- or parent-initiated OCS component.

Data collection and analysis

Two review authors independently screened the search results to identify any studies that met the prespecified inclusion criteria.

The prespecified primary outcomes were hospital admissions for asthma, asthma symptoms at follow-up and serious adverse events.

Main results

Despite comprehensive searches of electronic databases and clinical trial registries, we did not identify any studies meeting the inclusion criteria for this review. Five potentially relevant studies were excluded for two reasons: the intervention did not meet the inclusion criteria for this review (three studies) and studies had a cross-over design (two studies). Two of the excluded studies asked the relevant clinical question. However, these studies were excluded due to their cross-over design, as per the protocol. We contacted the authors of the cross-over trials who were unable to provide data for the first treatment period (i.e. prior to cross-over).

Authors' conclusions

There is currently no evidence from randomised trials (non-cross-over design) to inform the use of patient- or parent-initiated oral corticosteroids in people with asthma.

PLAIN LANGUAGE SUMMARY

Oral corticosteroid treatment started by patients or parents during a severe asthma attack

Background

Asthma is a long-term inflammatory disease of the airways affecting around 334 million people worldwide. During severe asthma attacks, people may need to visit a medical centre or hospital emergency department for treatment with corticosteroids, which may be given directly into a vein or by mouth. Some people with asthma are provided with oral steroids that they can take themselves (patient-initiated) or give to their child (parent-initiated) in the event of a severe asthma attack. This approach to treatment is becoming increasingly common.

Review question

We looked for studies comparing a) patient- or parent-initiated oral steroids with b) no patient- or parent-oral steroids (e.g. patient attends a medical centre or emergency department for further treatment by a doctor or nurse). The studies had to include either adults aged 18 years or older, or children of school age aged 5 years or older. Two review authors screened the search results independently of each other. The initial search was performed in May 2016.

Results

We screened 61 studies in total but we found no studies matching the above criteria. Five studies were excluded because the design of the studies was not allowed according to our review protocol. Two of these studies asked the correct clinical question but these studies were excluded because they used a type of trial design that was not allowed according to our review protocol.

Conclusions

There is currently a lack of evidence whether the use of patient- or parent-initiated oral steroids is safe or has a beneficial treatment effect in patients with asthma. This is a concern because this approach to treatment is becoming more common.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Patient-initiated steroids compared with placebo/normal care/alternative active treatment for asthma

Patient or population: adults aged 18 years or older with asthma
Settings: outpatient
Intervention: patient-initiated oral corticosteroids
Comparison: placebo/normal care/alternative active treatment

Outcomes	Number of participants (studies)	Comments
Hospital admissions for asthma	0 (0 studies)	No studies met the inclusion criteria for this review
Asthma control (validated scales)	0 (0 studies)	
Serious adverse events (all cause)	0 (0 studies)	
Unscheduled visit to a healthcare provider	0 (0 studies)	
Health-related quality of life (validated scales)	0 (0 studies)	
Days lost of study/work	0 (0 studies)	
Adverse events (all cause)	0 (0 studies)	

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

BACKGROUND

Description of the condition

Asthma is a chronic condition of the airways affecting an estimated 334 million people worldwide (Global Asthma Report 2014). Direct treatment costs and indirect costs associated with lost productivity are substantial and are among the highest for non-communicable diseases (Global Asthma Report 2014). Asthma triggers may be allergic or non-allergic, resulting in airway inflammation (including an eosinophilic and/or neutrophilic component), hyper-responsiveness and airflow obstruction. During a worsening of asthma symptoms (i.e. an exacerbation), which include tightness of the chest, wheeze and breathlessness, patients will typically exhibit an acute narrowing of the airway and reduced lung function (BTS/SIGN 2016). Impairment of lung function can be reversed with treatment and may return to normal. From a patient perspective, the goals of asthma treatment are to prevent exacerbations, achieve control of daytime and nocturnal symptoms, and permit normal exercise and functional capacity (GINA 2016). Treatment

of asthma should be guided by a personalised asthma action plan (GINA 2016), and includes the avoidance of potential triggers, the use of inhaled corticosteroids (ICS) or leukotriene receptor antagonists or both to reduce airway inflammation, and the use of inhaled long-acting beta$_2$-agonists (LABA), short-acting beta$_2$-agonists (SABA) and anti-cholinergic bronchodilators (i.e. long-acting muscarinic antagonists (LAMAs) to relieve airflow limitation (NICE 2007; NICE 2013; BTS/SIGN 2016; GINA 2016). During severe exacerbations, patients may need to attend a medical centre or hospital emergency department for treatment with systemic corticosteroids, which can be administered intravenously or orally (BTS/SIGN 2016; GINA 2016). Some people with asthma are prescribed oral corticosteroids (OCS) for self-administration (i.e. patient-initiated) or to administer to their child with asthma (i.e. parent-initiated), in the event of an exacerbation (Vuillermin 2007).

Description of the intervention

Prophylactic treatment with corticosteroids is commonly used in patients with asthma to reduce and control airway inflammation (BTS/SIGN 2016; GINA 2016), thus serving to improve asthma control and reduce future risks. ICS are used in preference to systemic corticosteroids because the inhaled dose is delivered directly to the respiratory tract (i.e. drug target), lowering the propensity for systemic side effects. Adverse effects associated with the long-term use of systemic steroids include: effects on bone density (e.g. osteoporosis and increased risk of femur neck fractures), growth retardation in children, a tendency to hyperglycaemia, and suppression of the response to infection or injury (Rang 2015). Recurrent short courses of prednisolone may also be associated with adverse events, in particular, with a reduction of bone mineral accrual as reported among participants in the Childhood Asthma Management Program (CAMP) trial (CAMP Research Group 2000; Kelly 2008). However, evidence supports the short-term use of systemic corticosteroids during acute asthma exacerbations (Rowe 2007; Fernandes 2014). Patients remain particularly prone to repeat exacerbations in the period immediately after an asthma exacerbation and the use of systemic steroids can reduce the risk of a relapse and the need for reliever inhalers, without major adverse effects (Rowe 2007). Prescription of a 'rescue pack' (containing a course of OCS) to a patient or their career permits self-administered treatment in the event of an exacerbation, as guided by a patient's personalised asthma action plan (BTS/SIGN 2016).

How the intervention might work

Patient-initiated OCS may feature as part of a written asthma action plan (GINA 2016), which should state when and how to initiate treatment with OCS, and when to access medical care if symptoms fail to respond to treatment. Compared with OCS administered by an emergency department physician, patient- or parent-initiated treatment permits early administration of systemic corticosteroids following the onset of an acute exacerbation. The benefits of OCS have been demonstrated within three hours of administration, and delayed dosing of OCS is less effective at resolving acute asthma (Streetman 2002). Indeed, there is some evidence from studies in children that early administration of systemic steroids during an exacerbation can reduce asthma symptoms and the number of days of missed school, compared with physician-initiated steroids (Vuillermin 2010). Furthermore, recurrent severe exacerbations are associated with accelerated lung function decline, suggesting that aggressive treatment of intermittent airway inflammation may be important to prevent airway remodelling (Bai 2007).

Why it is important to do this review

The use of patient-initiated oral steroids is common practice in chronic obstructive pulmonary disease (COPD) (DoH 2010) and the appropriate use of rescue packs is currently included in a National Institute for Health and Care Excellence (NICE) quality statement for managing COPD (NICE 2010). In line with their use in COPD, the use of patient- and parent-initiated OCS for asthma appears to be increasingly common in clinical practice (Vuillermin 2007; BTS/SIGN 2016). For example, in an Australian survey of 252 doctors involved in the care of children with asthma, 85% of doctors reported recommending parent-initiated OCS to parents of children with asthma (Vuillermin 2007). Additionally, British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines on personalised action plan content recommend coverage on starting oral steroids, "which may include provision of an emergency course of steroid tablets" (BTS/SIGN 2016). However, to date there is limited evidence for the use of patient- or parent-initiated OCS for treating asthma exacerbations (NACA 2015). An earlier Cochrane review evaluated the evidence around parent-initiated oral corticosteroid therapy for intermittent wheezing illnesses in children (Vuillermin 2006). We will not consider pre-school wheeze in the present review.

It is important to consider the potential benefits of earlier treatment with OCS against potential harms, which include the safety issues around delaying access to medical care when OCS are taken at home. Furthermore, the provision of rescue packs to patients with asthma or to their carers will likely increase overall administration of oral corticosteroids; this has implications for the incidence of steroid-associated side-effects, particularly in children. Taken together, this information highlights the importance of synthesising the evidence to establish whether this intervention is safe and effective in people with asthma.

OBJECTIVES

To evaluate the effectiveness and safety of patient- or parent-initiated oral steroids for adults and children with asthma exacerbations.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials (RCTs), reported as full-text, those published as abstract only, and unpublished data. We excluded cross-over trials because the effects of corticosteroids can persist for a number of weeks or months (Haahtela 1994) and studies did not employ a sufficient washout period between treatment periods to eliminate cross-over effects.

Types of participants

We planned to include adults (aged ≥ 18 years) and children of school age or older (i.e. aged ≥ 5 years) with a diagnosis of asthma. Adults and children were to be considered in separate comparisons. Preschool wheeze was not considered by this review and as such we excluded studies of preschool children. The diagnosis of asthma was required to be determined by a clinician according to validated national or international guidelines. We excluded participants with any respiratory comorbidities (e.g. bronchiectasis, chronic obstructive pulmonary disease). If a study contained both adults and children, we contacted the study authors to check if disaggregated data were available; if we were unable to source these data we used the average age (≥ 18 years) of study participants to determine suitability for inclusion. If the average age of study participants was less than 18 years, we planned to perform a sensitivity analysis to examine the effect of including or excluding these studies. Finally, if a study included children of both school and preschool age, we excluded the study if the average age was less than five years old.

Types of interventions

We planned to include studies comparing any patient- or parent-initiated oral corticosteroid (OCS), with either placebo, normal care, an alternative active treatment plan (e.g. doubling the dose of inhaled steroids) or an identical personalised asthma exacerbation management plan without patient- or parent-initiated OCS. OCS (any dose or duration) could be combined with other measures for the management of an exacerbation (e.g. personalised asthma action plan, increased use of reliever inhaler) provided that the measure was not part of the randomised treatment. We planned to perform separate comparisons for each type of comparator (e.g. patient-initiated steroids versus placebo; patient-initiated steroids versus normal care, etc); separate comparisons would also be performed for adults and children. We defined normal care as any measure that the patient would usually take to manage an exacerbation (e.g. increase reliever inhaler use, seek medical advice, etc). We also planned to include studies where the comparator group comprised a combination of the above (e.g. personalised asthma action plan plus placebo).

Types of outcome measures

Primary outcomes

1. Hospital admissions for asthma.
2. Asthma symptoms at follow-up (measured on a validated scale (e.g. Asthma Control Questionnaire (ACQ))).
3. Serious adverse events.

We selected the primary outcomes to represent an important measure of resource use, a patient-reported outcome, and safety.

Secondary outcomes

1. Unscheduled visit to a healthcare provider (e.g. accident and emergency, general practitioner).
2. New exacerbation in follow-up period (asthma control).
3. Health-related quality of life (using a validated scale).
4. Reliever medication use.
5. Days of school (children) or study/work (adults) lost.
6. Time to full resolution of symptoms.
7. Adverse events.

Reporting one or more of the outcomes listed here in the study was not an inclusion criterion for the review. If a study used more than one scale to report the same outcome, or if different scales were used across studies, we planned to analyse the different scales together using the standardised mean difference.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group's Specialised Register (CAGR) (searched 18 May 2016), which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4) in the Cochrane Library; MEDLINE Ovid; Embase Ovid; CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; AMED Ovid (Allied and Complementary Medicine; and PsycINFO Ovid; and handsearching of respiratory journals and

meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR using the search strategy in Appendix 2. We also conducted a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 24 August 2016) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 24 August 2016).

When searching all databases we imposed no restriction on language of publication.

Searching other resources

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

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

Data collection and analysis

Selection of studies

Two review authors (MBG, MG) independently screened titles and abstracts of all the potentially-relevant studies that we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publication and two review authors (MBG, MG) independently screened the full-text articles to confirm studies for inclusion, or to identify and record reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third review author (MM). We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We recorded 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 planned to use a data collection form for study characteristics and outcome data, which would be piloted on at least one study in the review. Two review authors (MBG, DE) planned to extract study characteristics from included studies. We planned to extract the following study characteristics.

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

Two review authors (MBG, DE) planned to independently extract outcome data from the included studies. We planned to note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We planned to resolve disagreements by consensus or by involving a third review author (MM). One review author (DE) was responsible for transferring data into the Review Manager (RevMan 2014) file. We planned to double-check that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (DE) was responsible for spot-checking study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (MBG, DE) planned to independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to resolve any disagreements by discussion or by involving another review author (MM). We planned to 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 planned to grade 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 planned to summarise the 'Risk of bias' judgements across different studies for each of the domains listed, and to 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 planned to note this in the 'Risk of bias' table.

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

Assesment of bias in conducting the systematic review

We conducted the review according to the published protocol (Ganaie 2016) and reported any deviations from it in the 'Dif-

ferences between protocol and review' section of the systematic review.

Measures of treatment effect

We planned to analyse dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We planned to enter data presented as a scale with a consistent direction of effect.

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

We planned to narratively describe skewed data reported as medians and interquartile ranges.

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

Unit of analysis issues

For dichotomous outcomes, we planned to report participants, rather than events, as the unit of analysis. For example, for the secondary outcome 'unscheduled visit to a healthcare provider' we would record the number of participants with an unscheduled visit, rather than the number of unscheduled visits per participant.

Dealing with missing data

We planned to 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 was identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by conducting a sensitivity analysis**.**

Assessment of heterogeneity

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

Assessment of reporting biases

If we were able to pool more than 10 studies, we planned to create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We planned to use a random-effects model and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We created a 'Summary of findings' table for each comparison using the following outcomes: hospital admissions for asthma; asthma symptoms at follow-up; serious adverse events; unscheduled visit to a healthcare provider; asthma control at follow-up; days of school or study/work lost; and adverse events. We planned to use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Guyatt 2011). We planned to use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro GDT software (GRADEpro GDT). We planned to justify all decisions to downgrade or upgrade the quality of studies using footnotes and to make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Baseline asthma severity (stratified by background medication).

We planned to use the following outcomes in subgroup analyses.

1. Hospital admissions for asthma.
2. Asthma symptoms at follow-up.
3. Serious adverse events.

We planned to use the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

If necessary, we planned to carry out the following sensitivity analyses to explore the effect of including/excluding:

1. studies that included both adults and children/adolescents, where the average age of participants was < 18 years;
2. unpublished data (i.e. no peer-reviewed full-text paper available);
3. studies at high risk of performance or detection bias;
4. studies at high risk of any other bias;
5. studies with missing data.

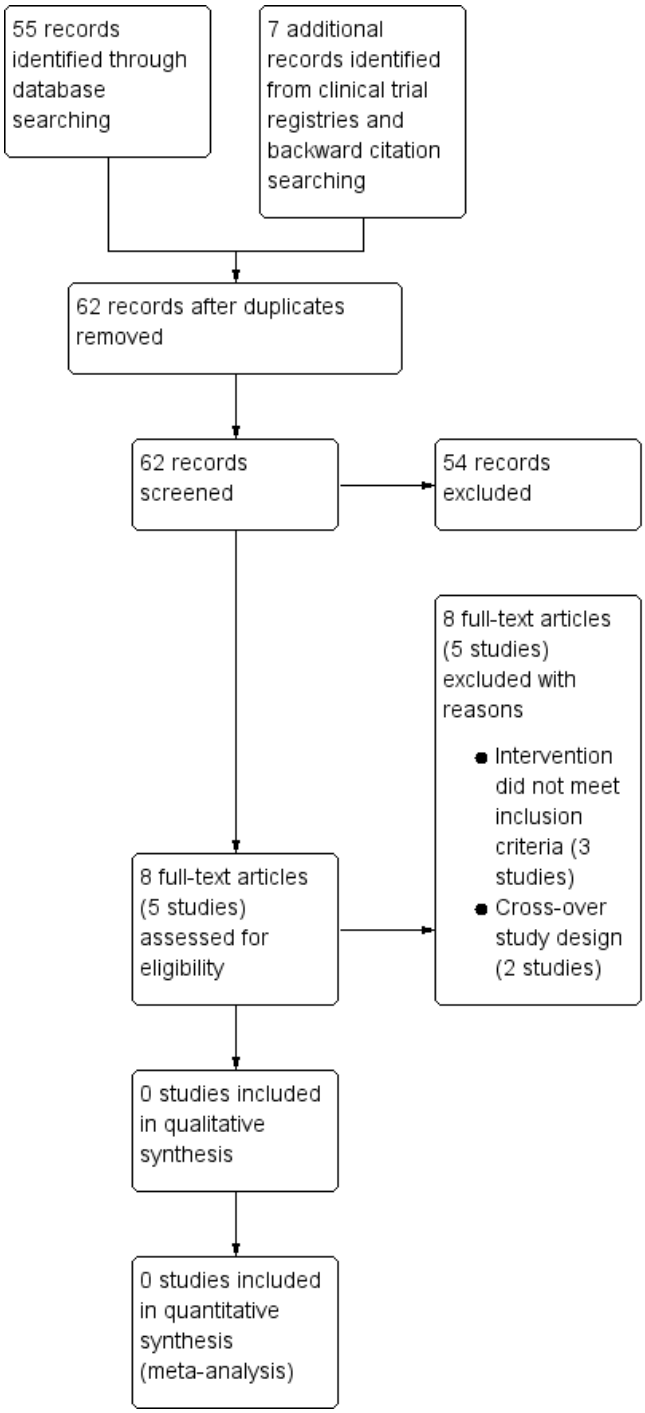
RESULTS

Description of studies

Results of the search

A search of the Cochrane Airways' Specialised Register (CASR) returned 55 references and the search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform yielded a further 7 records. Two review authors screened the 62 references/records using Covidence (Covidence 2016) and 54 records were discarded. We selected eight references (five studies) as potential candidates for inclusion in this review and sourced the corresponding full-text articles. Two review authors screened the full-text articles independently and all five studies were excluded with reasons. The PRISMA flow diagram is presented in Figure 1.

Figure 1. Study flow diagram.



Included studies

We included no studies.

Excluded studies

We excluded five studies with reasons (see Characteristics of excluded studies table). Three studies were excluded because the intervention did not meet the criteria for inclusion in this review (oral corticosteroids (OCS) must be part of the randomised treatment and could be combined with other measures for the management of an exacerbation such as a personalised asthma action plan, provided that the co-intervention was not part of the randomised treatment). Specifically, the OCS were not part of the randomised treatment in the study by Boushey 2005. Participants in the study reported by Milenović 2007 could initiate oral corticosteroids as per a personalised asthma action plan (i.e. co-intervention), which was part of the randomised treatment and was not available to participants in the control group. In van Der Meer 2009, the oral corticosteroids were optional at step seven of an internet-based asthma plan (i.e. co-intervention), which was part of the randomised treatment. Furthermore, the oral corticosteroids were taken following contact with an asthma nurse, and the usual care group received no plan. Two studies were excluded because of their cross-over design (Grant 1995; Vuillermin 2010); we contacted the authors of the respective studies, who were unable to provide data for the first treatment period (i.e. prior to cross-over).

Risk of bias in included studies

Not applicable.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: patient-initiated steroids; **Summary of findings 2** Summary of findings: parent-initiated steroids

Not applicable.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Parent-initiated steroids compared with placebo/normal care/alternative active treatment for asthma		
Patient or population: children aged 5 years or older with asthma **Settings:** outpatient **Intervention:** parent-initiated oral corticosteroids **Comparison:** placebo/normal care/alternative active treatment		
Outcomes	**Number of participants (studies)**	**Comments**
Hospital admissions for asthma	0 (0 studies)	No studies met the inclusion criteria for this review
Asthma control (validated scales)	0 (0 studies)	
Serious adverse events (all cause)	0 (0 studies)	
Unscheduled visit to a healthcare provider	0 (0 studies)	
Health-related quality of life (validated scales)	0 (0 studies)	
Days off school	0 (0 studies)	
Adverse events (all cause)	0 (0 studies)	
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate		

DISCUSSION

Summary of main results

After screening the results of extensive searches, we identified no relevant randomised controlled trials to include in this review. Five potentially relevant studies were excluded based on our pre-specified criteria. Two of the excluded studies asked the relevant clinical question (Grant 1995; Vuillermin 2010). However, these studies were excluded due to their cross-over design, as per the protocol. The authors were contacted but were unable to provide data for the first treatment period only (i.e. prior to cross-over).

Overall completeness and applicability of evidence

We identified no relevant studies to include in this review.

Quality of the evidence

Despite performing a comprehensive search and a duplicate (independent) screening and reviewing process, we identified no relevant studies to include in this review.

Potential biases in the review process

This review process could potentially be subject to a risk of bias in two areas: searching and drawing conclusions. However, Cochrane Airways' Information Specialist designed and conducted the main electronic search and two clinicians in the author team (MG, MBG) with expert knowledge in the area independently sifted and reviewed the search results. Consistent with Cochrane methodology, we excluded no trials on the basis of language, publication status, or the outcomes reported, so we are confident that we identified all potentially relevant randomised evidence. Our conclusions are consistent with the lack of included studies.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no existing systematic reviews on this topic. The two randomised controlled trials that asked the relevant clinical question, but were excluded from the present review due to their cross-over design, reported contrasting findings. Grant and colleagues examined the effectiveness of a single oral dose of prednisone administered by a parent to a child early in an asthma attack (Grant 1995). Contrary to expectation, the authors found that participants in the parent-initiated oral prednisone group had significantly more asthma exacerbations resulting in outpatient visits than when they were in the placebo group (Grant 1995). The authors speculated that the results may be specific for a population of children with suboptimal use of beta-agonist therapy, and stressed that further studies are required in different populations of asthmatic children (Grant 1995). In contrast, Vuillermin and colleagues found that among children of school age, a short course of parent-initiated oral prednisolone during an asthma exacerbation may result in a reduction in asthma symptoms, health resource use, and days off school (Vuillermin 2010). However, the authors cautioned that the modest benefits of this strategy should be balanced against potential side effects of repeated oral corticosteroid use (Vuillermin 2010).

AUTHORS' CONCLUSIONS

Implications for practice

A previous Cochrane review found that a short course of corticosteroids following assessment for an asthma exacerbation significantly reduced the number of relapses requiring additional care, hospitalisations and the use of short-acting beta$_2$-agonists, without an apparent increase in side effects (Rowe 2007). However, there is currently no evidence to support the use of patient- or parent-initiated oral corticosteroids (OCS) in the event of an asthma exacerbation.

Asthma is characterized by chronic airway inflammation, that is predominantly eosinophilic and corticosteroid-sensitive. However long-term adherence to inhaled corticosteroids (ICS) is typically low in clinical practice, which can lead to suboptimal asthma control and asthma exacerbations (Weinstein 2015). Hence, in any patient-initiated OCS strategy, it is crucial to ascertain patient compliance to ICS and optimal inhaler technique. In mild-moderate asthma cases, a Single Maintenance And Reliever Therapy (SMART) approach is an alternative option that allows for patient autonomy in self-titration of ICS, and has been shown to improve asthma control and reduce need for exacerbations requiring OCS, though it did not reduce hospitalisation rates (Cates 2013). However, only a relatively small proportion of patients on SMART are controlled and many continue to have eosinophilic inflammation (Chapman 2010). In severe asthma, where up to 50% of the patients have non-eosinophilic airway inflammation, sputum-guided titration of treatment is shown to reduce exacerbations (Petsky 2012). In view of these real-life issues, patient-initiated OCS might pose problems for misuse and abuse, if doctors do not first ensure that their patients are adherent to ICS and that severe asthma cases are not relegated to recurrent OCS bursts when they might be suitable for novel biologics or bronchial thermoplasty, depending on patient-specific disease mechanisms.

In conclusion, though guidelines recommend that written asthma action plans consider patient-initiated OCS, to facilitate early treatment of a significant asthma exacerbation, current evidence is scarce.

Implications for research

A double-blind, parallel-arm, randomised controlled trial to assess this question would help clinicians to judge whether it is safe and effective for parents or patients to initiate treatment with oral corticosteroids in the event of an asthma exacerbation. Ideally, at least one adequately powered trial would be performed in each of the relevant age groups (children and adolescents; adults). Additionally, future studies would include mild-moderate asthma cases, objectively monitor patient ICS adherence rates and, if feasible, measure blood and airway eosinophilia at baseline and during an exacerbation. We would recommend that future trials on this topic do not use a cross-over design due to concerns around the elimination of cross-over effects.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Boushey 2005	OCS was not part of the randomised treatment
Grant 1995	Cross-over design
Milenovic 2007	OCS was administered as part of asthma action plan (i.e. co-intervention), which was part of randomised treatment
van Der Meer 2009	OCS could be optionally administered as part of asthma action plan, which was part of randomised treatment
Vuillermin 2010	Cross-over design

OCS = oral corticosteroids.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

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

Electronic searches: core databases

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

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards

(*Continued*)

European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

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

Filter to identify randomised controlled trials (RCTs)

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

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

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

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 prednis*
#6 methylprednis*
#7 dexamethasone
#8 cortisone
#9 hydrocortisone*
#10 medrol
#11 solumedrol
#12 solu-medrol
#13 betamethasone
#14 triamcinolone
#15 (oral* or systemic*) near3 (steroid* or corticosteroid* or glucocorticoid*)
#16 OCS:ti,ab
#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 MeSH DESCRIPTOR Patient Participation
#19 MeSH DESCRIPTOR Decision Making
#20 (patient* or parent* or caregiver* or career*) NEAR (initiat* or suggest* or instigat* or originat* or request* or propose* or encourage* or advocate*)
#21 self-refer* or self NEXT refer*
#22 #18 or #19 or #20 or #21
#23 #4 AND #17 AND #22
#24 (#23) AND (INREGISTER)
(Note: in search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, asthma)

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the drafting of the review, reviewed it critically for intellectual content, provided final approval of the version to be published and are accountable for all aspects of the work.

DECLARATIONS OF INTEREST

MB Ganaie: none known.

M Munavvar: none known.

M Gordon: none known.

HF Lim: none known.

D Evans: provides freelance writing services to medical communication agencies.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review was performed as per the protocol. We substituted one of the secondary outcomes for health-related quality of life as the outcome in question (asthma control) was already included as a primary outcome.