Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department (Review)

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[Intervention Review]

Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

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ABSTRACT

Background

Asthma is a chronic respiratory condition characterised by airways inflammation, constriction of airway smooth muscle and structural alteration of the airways that is at least partially reversible. Exacerbations of asthma can be life threatening and place a significant burden on healthcare services. Various guidelines have been published to inform management personnel in the acute setting; several include the use of a single bolus of intravenous magnesium sulfate (IV $MgSO_4$) in cases that do not respond to first-line treatment. However, the effectiveness of this approach remains unclear, particularly in less severe cases.

Objectives

To assess the safety and efficacy of IV $MgSO_4$ in adults treated for acute asthma in the emergency department.

Search methods

We identified trials from the Cochrane Airways Review Group Specialised Register (CAGR) up to 2 May 2014. We also searched www.ClinicalTrials.gov and reference lists of other reviews, and we contacted trial authors to ask for additional information.

Selection criteria

We included randomised controlled trials (RCTs) of adults treated in the emergency department (ED) for exacerbations of asthma if they compared any dose of IV $MgSO_4$ with placebo.

Data collection and analysis

All review authors screened titles and abstracts for inclusion, and at least two review authors independently extracted study characteristics, risk of bias and numerical data. Disagreements were resolved by consensus, and we contacted trial investigators to obtain missing information.

We analysed dichotomous data as odds ratios using study participants as the unit of analysis, and we analysed continuous data as mean differences or standardised mean differences using fixed-effect models. We rated all outcomes using GRADE and presented results in Summary of findings table 1.

We carried out subgroup analyses on the primary outcome for baseline severity of exacerbations and whether or not ipratropium bromide was given as a co-medication. Unpublished data and studies at high risk of bias for blinding were removed from the main analysis in sensitivity analyses.

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Main results

Fourteen studies met the inclusion criteria, randomly assigning 2313 people with acute asthma to the comparisons of interest in this review.

Most studies were double-blinded trials comparing a single infusion of 1.2 g or 2 g IV $MgSO_4$ over 15 to 30 minutes versus a matching placebo. Eleven were conducted at a single centre, and three were multi-centre trials. Participants in almost all of the studies had already been given at least oxygen, nebulised short-acting $beta_2$-agonists and IV corticosteroids in the ED; in some studies, investigators also administered ipratropium bromide. Ten studies included only adults, and four included both adults and children; these were included because the mean age of participants was over 18 years.

Intravenous $MgSO_4$ reduced hospital admissions compared with placebo (odds ratio (OR) 0.75, 95% confidence interval (CI) 0.60 to 0.92; I^2 = 28%, P value 0.18; n = 972; high-quality evidence). In absolute terms, this odds ratio translates into a reduction of seven hospital admissions for every 100 adults treated with IV $MgSO_4$ (95% CI two to 13 fewer). The test for subgroup differences revealed no statistical heterogeneity between the three severity subgroups (I^2 = 0%, P value 0.73) or between the four studies that administered nebulised ipratropium bromide as a co-medication and those that did not (I^2 = 0%, P value 0.82). Sensitivity analyses in which unpublished data and studies at high risk for blinding were removed from the primary analysis did not change conclusions.

Within the secondary outcomes, high- and moderate-quality evidence across three spirometric indices suggests some improvement in lung function with IV $MgSO_4$. No difference was found between IV $MgSO_4$and placebo for most of the non-spirometric secondary outcomes, all of which were rated as low or moderate quality (intensive care admissions, ED treatment duration, length of hospital stay, readmission, respiration rate, systolic blood pressure).

Adverse events were inconsistently reported and were not meta-analysed. The most commonly cited adverse events in the IV $MgSO_4$ groups were flushing, fatigue, nausea and headache and hypotension (low blood pressure).

Authors' conclusions

This review provides evidence that a single infusion of 1.2 g or 2 g IV $MgSO_4$ over 15 to 30 minutes reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulised short-acting $beta_2$-agonists and IV corticosteroids. Differences in the ways the trials were conducted made it difficult for the review authors to assess whether severity of the exacerbation or additional co-medications altered the treatment effect of IV $MgSO_4$. Limited evidence was found for other measures of benefit and safety.

Studies conducted in these populations should clearly define baseline severity parameters and systematically record adverse events. Studies recruiting participants with exacerbations of varying severity should consider subgrouping results on the basis of accepted severity classifications.

PLAIN LANGUAGE SUMMARY

Do magnesium sulfate infusions reduce the need for hospital admission in adults with acute asthma?

Why is this question important?

Asthma is a long-term condition that causes coughing, wheezing, shortness of breath and chest tightness. When symptoms significantly worsen, often referred to as an attack or 'exacerbation,' this can be life threatening. Management of exacerbations in the emergency department (ED) varies, and some guidelines recommend the use of intravenous magnesium sulfate (IV $MgSO_4$) when other treatments have not helped. However, it is unclear whether IV $MgSO_4$ is effective, particularly in less severe cases, and we wanted to answer this question.

How did we answer the question?

We looked for trials that compared IV $MgSO_4$ versus placebo in adults attending the ED with an asthma exacerbation. The most recent searches were done on 2 May 2014. We were interested primarily in whether IV $MgSO_4$ reduced the number of people needing to be admitted to hospital, and we looked at several other measures as well, including time spent in the ED, lung function and symptom scores.

What did we find?

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Fourteen studies met the inclusion criteria, involving a total of 2313 people. These studies varied in terms of how bad exacerbations had to be for people to be included and in terms of what other treatments were provided before IV $MgSO_4$was given, but almost all trials gave participants at least oxygen, nebulised short-acting medications and steroid tablets or injection.

Overall, IV $MgSO_4$ reduced the need for hospital admission compared with placebo (seven fewer per 100 treated; 95% confidence interval two to 13 fewer). Not enough information was available to show whether the reduction in hospital admissions was associated with severity of the asthma exacerbation, or whether it made a difference what other treatments were given. Evidence suggests that IV $MgSO_4$ improved some lung function parameters, but for other measures such as heart rate, variation among study findings reduced our confidence in the results. We did not find a difference between IV $MgSO_4$ and placebo in most other measures (including time spent in the ED, respiratory rate and blood pressure), and adverse events generally were poorly reported.

Conclusion

This review showed that IV $MgSO_4$ reduces hospital admissions and improves lung function in adults with exacerbations of asthma when other first-line medications have not relieved the acute symptoms (i.e. oxygen, inhaled short-acting medications and IV steroids). Evidence for other measures of benefit and safety was limited.

Researchers should clearly define the severity of the asthma condition among people in their studies while carefully recording adverse events.

This plain language summary is current as of May 2014.

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

IV $MgSO_4$ for treating adults with acute asthma in the ED

Patient or population: adults with acute asthma
Settings: emergency department
Intervention: IV $MgSO_4$
Comparions: placebo
Both intervention and placebo groups received oxygen, short-acting $beta_2$-agonists and oral or intravenous steroids before the infusion
Measurements were taken between 60 and 240 minutes after the start of the infusion

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	IV $MgSO_4$			
Hospital admissions	**569 per 1000**	**498 per 1000** (442 to 549)	**OR 0.75** (0.60 to 0.92)	1769 (11 studies)	⊕⊕⊕⊕ **high**[1,2]
Intensive care unit (ICU) admissions	**14 per 1000**	**28 per 1000** (10 to 77)	**OR 2.03** (0.7 to 5.89)	752 (1 study)	⊕⊕◯◯ **low**[3,4]
Length of hospital stay (days)	Mean length of hospital stay in the control groups was **2.73 days**[5]	Mean length of hospital stay in the intervention groups was **0.03 days lower** (0.33 lower to 0.27 higher)	-	949 (3 studies)	⊕⊕◯◯ **low**[6,7,8]
ED treatment duration (minutes)	Mean duration in the placebo group was **228 minutes**	Mean ED treatment duration in the intervention groups was **4 minutes lower** (37.02 lower to 29.02 higher)	-	96 (1 study)	⊕⊕◯◯ **low**[9,10,11]
FEV_1 (% predicted)	Mean FEV_1 in the placebo group was **50% predicted**	Mean FEV_1 (% predicted) in the intervention groups was **4.41 higher** (1.75 to 7.06 higher)	-	523 (4 studies)	⊕⊕⊕⊕ **high**[12,13,14]

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PEF (L/min)	Mean PEF in the placebo group was **239 L/min**	Mean PEF in the intervention groups was **17.4 L/min higher** (8.64 to 26.17 higher)	-	1460 (8 studies)	⊕⊕⊕◯ **moderate**[15,16,17]
Respiratory rate (breaths/min)	Mean respiration rate in the placebo group was **20.7 respirations/min**	Mean respiratory rate in the intervention groups was **0.28 breaths/min lower** (0.77 lower to 0.2 higher)	-	1195 (4 studies)	⊕⊕⊕◯ **moderate**[18,19,20]

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **ED**: Emergency department; **FEV_1** : Forced expiratory volume in 1 second; **ICU**: Intensive care unit; IV: Intravenous; $MgSO_4$: Magnesium sulfate; **OR**: Odds ratio; **PEF**: Peak expiratory flow.

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.

[1]One study (Green 1992) introduced risk of bias, but the rest of the studies were generally well conducted.
[2]I^2 = 28%; P value 0.18; not statistically significant.
[3]Confidence interval includes potential benefit and harm. Very few events and only 1 study (-2 for imprecision).
[4]Only 1 study (Goodacre 2013) reported this outcome, but no other studies set out to measure it at the outset.
[5]Weighted by sample size.
[6]Two of the 3 studies were at high risk of bias for blinding, and there were some issues with selection bias.
[7]I^2 = 58%; P value 0.07, suggesting statistically significant heterogeneity.
[8]Although only 3 studies reported this outcome, it was not named as an outcome in other studies.
[9]Only 1 study (Green 1992), which was assessed as having high risk of bias for several domains.
[10]Only 1 study (Green 1992), which had wide confidence intervals (-37.02 to 29.02).
[11]Only 1 study reported ED treatment duration, but it was not named as an outcome in other studies.
[12]Only 1 study (Bilaceroglu 2001) had the potential for risk of bias, but all other studies were low risk and included large numbers of participants.
[13]No significant heterogeneity was noted (I^2 = 14%; P value 0.33).
[14]Moderately wide confidence interval (1.75 to 7.06), but after discussion, review authors decided that no downgrade was required.

[15]Two studies (Green 1992; Matusiewicz 1994) had 'unclear' and 'high' risk of bias, respectively. However, the remaining 6 studies were of low risk and contributed most of the participant numbers.
[16]Some heterogeneity between the studies, which was statistically significant (I^2 = 50%; P value 0.05). However, when random effects were applied, conclusions were not changed.
[17]Wide confidence intervals (8.64 to 26.17), but does not cross zero.
[18]Very little heterogeneity observed between the studies (I^2 = 1%), which was not significant (P value 0.39).
[19]Confidence interval (-0.77 to 0.20) includes significant benefit and potential harm (i.e. crosses the line of no effect).
[20]Only 4 studies reported respiratory rate, but it was not named as an outcome in other studies.

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BACKGROUND

Description of the condition

Asthma is a chronic respiratory condition characterised by airway inflammation, constriction of airway smooth muscle and structural alteration of the airways that is at least partially reversible. Common symptoms include cough, wheezing, difficulty breathing, reduced exercise tolerance and chest tightness. Common triggers include allergens, pollutants and viral infections, although endogenous factors have also been identified. The World Health Organization (WHO) recognises the global burden of asthma and estimates a worldwide prevalence of 300 million people of all ages, with 250,000 dying each year. Epidemiological data suggest that prevalence is greatest in the developed world, with prevalence amongst adults at 8.2% in the USA (CDC) and 9% to 10% in the UK (DOH 2012).

Asthma can present with varying degrees of severity, and in the most severe cases, it can cause daily chronic symptoms and frequent exacerbations (defined as acute worsening of asthma symptoms). Overarching principles of treatment focus on controlling daily symptoms and preventing exacerbations through good education and appropriate use of inhalers. Short-acting bronchodilators are given to relieve bronchospasm, and corticosteroids for the underlying inflammation; both are usually delivered via inhalers. Depending on the persistence of symptoms, inhalers can be taken regularly (maintenance therapy) or on an as-needed basis (reliever therapy) (BTS/SIGN 2012; GINA 2011). Treatment guidelines recommend preventative management in the community and prompt interventions during exacerbations to reduce mortality and other negative outcomes (such as intubation and hospital admissions).

Description of the intervention

In severe exacerbations of asthma, which can be life threatening, most guidelines recommend the use of oxygen, nebulised or intravenous beta$_2$-agonists, nebulised antimuscarinics and intravenous or oral corticosteroids as first-line treatment (BTS/SIGN 2012; GINA 2011; NACA 2006; NAEPP 2007). Beta$_2$-agonists are recognised as most effective in relieving bronchospasm (Teoh 2012); however, anticholinergic inhalers have also been shown to be effective in the treatment of acute asthma (Griffiths 2013). When patients show poor response to these, or when they present with a severe or life-threatening exacerbation, a single dose of intravenous (IV) or nebulised magnesium sulfate ($MgSO_4$) can be considered. Nebulised $MgSO_4$ is the subject of a separate review (Powell 2012). The recommended dosage of IV $MgSO_4$ in the UK is 1.2 g to 2 g, delivered by infusion over 20 minutes (BTS/SIGN 2012), but guidelines differ regarding how and when IV $MgSO_4$ should be administered (Table 1),

National guidelines also vary with respect to definitions of asthma severity and use of additional interventions. Table 1 offers a summary of treatment strategies recommended by some of these guidelines for the management of acute asthma.

How the intervention might work

Magnesium is an important intracellular and extracellular cation that plays a key role in intracellular enzymatic reactions. Its mechanism of action in the context of an exacerbation of asthma is not fully understood, but several theories have been proposed (Rowe 2013). It is believed to play a role in bronchial smooth muscle relaxation via its ability to prevent calcium ion movement into smooth muscle cells by blocking the voltage-dependent calcium channels (Gourgoulianis 2001; Spivey 1990). Furthermore, some evidence suggests that it may reduce the neutrophilic burst seen with the inflammatory response (Cairns 1996), and that it may be involved in acetylcholine release from cholinergic nerve terminals and histamine release from mast cells (Dominguez 1998). The combination of these properties contributes to relief of airflow obstruction and provides the theoretical basis for the effectiveness of magnesium.

Why it is important to do this review

Acute asthma presentations represent a significant burden on emergency departments (EDs) and carry a substantial mortality risk, with 1143 deaths from asthma reported in the UK in 2010 (Asthma UK) and an estimated mortality rate of 1.1 deaths per 100,000 in the USA (CDC). In the UK, it is thought that "75% of hospital admissions for asthma are avoidable and as many as 90% of the deaths from asthma are preventable" (Asthma UK). The financial burden is also significant, with a cost to the National Health Service (NHS) of £1 billion a year, 80% of which is spent on the 20% of people with the most severe disease (DOH 2012). Current guidelines advocate the use of IV $MgSO_4$ in the treatment of acute severe asthma, but evidence in the literature remains inconclusive (Rowe 2009). New evidence from randomised controlled trials published since the last version of this review may alter the conclusions.

OBJECTIVES

To assess the safety and efficacy of IV $MgSO_4$ in adults treated for acute asthma in the emergency department.

METHODS

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Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of any follow-up duration reported as full text, those published as abstract only and unpublished data.

Types of participants

We included studies of adults (defined as over 18 years of age) treated in the ED for acute asthma. If studies recruited both adults and children, we contacted the study authors to try to obtain separate data from adults.

Types of interventions

We included trials comparing any dose of IV $MgSO_4$ versus placebo. People with acute asthma often require multiple medications; therefore we included studies that allowed other treatments (for maintenance, for exacerbation itself or for other co-morbidities), provided they were not part of the randomly assigned treatment.

Types of outcome measures

Primary outcomes

- Hospital admissions.

Secondary outcomes

- ED treatment duration.
- Intensive care unit admissions.
- Vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation).
- Spirometry (peak expiratory flow (PEF), forced expiratory volume within one second (FEV_1)).
- Validated symptom scores.
- Adverse events.

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

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Review Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR using the search strategy described in Appendix 2.

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

Searching other resources

We checked reference lists of all relevant primary studies and review articles for additional references. We also searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and reported within the review the date this was done.

Data collection and analysis

Selection of studies

Three review authors (KK, LK, CM) independently screened titles and abstracts for inclusion of all citations identified by the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve.' We retrieved the full-text study reports/publications, and the review authors independently screened the full-text documents and identified studies for inclusion. We identified and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion, or, if required, we consulted a fourth person. We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a Characteristics of excluded studies table.

Data extraction and management

To record study characteristics and outcome data, we used a data collection form that had been piloted on at least one study in the review. All review authors (KK, LK, CM) extracted study characteristics from included studies, and all review authors independently extracted outcome data. We extracted the following study characteristics.

- Methods: study design, duration of observation and follow-up, details of any 'run-in' period, number of study centres and locations, withdrawals, dates of study.

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- Participants: N, mean age, age range, gender, asthma severity*, diagnostic criteria, co-morbidities, co-medications, baseline lung function, inclusion and exclusion criteria.
- Interventions: intervention, dose, comparison, concomitant and failed treatments, excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, time points reported.
- Notes: funding for trial, notable conflicts of interest of trial authors.

We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by reaching consensus or by involving a fourth person. One review author transferred data into the Review Manager (RevMan) (version 5.2) file. We double-checked that data were entered correctly by comparing data presented in the systematic review versus data provided in the study reports. A second review author (LK or CM) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

All review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), resolving disagreements by discussion. We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the Risk of bias in included studies table. We summarised risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for hospital admission may be very different than for a patient-reported scale). When information on risk of bias was related to unpublished data or correspondence with a trial author, we noted this in the Risk of bias in included studies table.
When considering treatment effects, we took into account the risk of bias for all studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios (ORs) and continuous data as mean differences (MDs) or standardised mean differences (SMDs) with 95% confidence intervals (CIs). If studies reported several validated symptom measures, or if different scales were reported across studies, we analysed the data as SMDs in one analysis to reduce measurement error and to increase precision. We entered data presented as a scale with a consistent direction of effect. We narratively described skewed data reported as medians and interquartile ranges.
We undertook meta-analyses only when this was meaningful (i.e. when treatments, participants and the underlying clinical question were similar enough for pooling to make sense).
When multiple trial arms were reported in a single trial, we included only the relevant arms. When two relevant comparisons from a single study were combined in the same meta-analysis, we halved the control group to avoid double-counting.

Unit of analysis issues

For dichotomous outcomes, we used participants rather than events as the unit of analysis (i.e. number of adults admitted to hospital rather than number of admissions per adult).

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 a study was identified as abstract only). When this was not possible, and when missing data were thought to introduce serious bias, we conducted a sensitivity analysis to explore the impact of including such studies in the overall assessment of results.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. When substantial heterogeneity was identified, we explored possible causes by conducting prespecified subgroup analyses.

Assessment of reporting biases

We created and examined a funnel plot to explore possible small-study and publication biases. We considered the impact of unpublished trials in the GRADE ratings for each outcome.

Data synthesis

We used a fixed-effect model and performed a sensitivity analysis with random effects when significant heterogeneity was observed ($I^2 > 30\%$).

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Summary of findings table

We created Summary of findings for the main comparison for seven of the prespecified outcomes. We used 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 that contributed data to meta-analyses for the prespecified outcomes (http://www.gradeworkinggroup.org/). We applied methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We carried out the following subgroup analyses for the primary outcome, using the formal test for subgroup differences in Review Manager (version 5.2) (Review Manager (RevMan)).

- Baseline severity (moderate, severe and life-threatening exacerbations*).
- Mean age (≤ and > 65 years).
- Co-medications (with or without ipratropium bromide**).

*Since there is no single accepted metric for assessment of asthma severity, we extracted baseline data relevant to the severity criteria, as stated in the British Thoracic Society (BTS) guidelines (BTS/SIGN 2012), that is,

- Clinical features (e.g. ability to complete sentences, respiratory effort, conscious level, signs of exhaustion);
- Previous intensive care unit admissions;
- Pulse;
- Blood pressure;
- Respiratory rate;
- Pulse oximetry;
- Pulsed expiratory flow (PEF); and
- Arterial blood gas.

Exacerbations of the study populations were labelled as moderate, severe or life threatening on the basis of available data, as judged by an independent assessor who was not involved in the review process and had no other details or results of the trials. Consistent with British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) criteria (BTS/SIGN 2012), for which the percentage predicted PEF was available, mean values less than 33% were judged to be life threatening, 33% to 50% severe and over 50% moderate. When this measure was not available, or when the value was close to a cutoff, other criteria were consulted, and the value was then standardised across trials using studies reporting several indices. The decision to perform a subgroup analysis by severity was informed by conclusions drawn in the previous Cochrane review (Rowe 2009) that the intervention may be more effective in cases of severe or life-threatening asthma.

**For co-medications, we grouped studies by whether investigators gave ipratropium bromide in addition to other treatments (i.e. short-acting beta$_2$-agonists (SABAs) via a nebuliser or spacer, oral or intravenous corticosteroids). Ipratropium bromide is included in most guidelines, but it is unclear whether this treatment is adopted in all EDs. Griffiths 2013 has demonstrated that it is an effective adjunct to SABAs in children with asthma exacerbation in the acute setting.

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

- Studies at high risk of bias for blinding.
- Unpublished data.

Reaching conclusions

We have based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We have avoided making recommendations for practice, and our implications for research suggest priorities for future research and outline remaining uncertainties in this area.

RESULTS

Description of studies

Full details of the conduct and characteristics of each included study can be found in Characteristics of included studies, and reasons for exclusion when full texts had to be viewed are given in Characteristics of excluded studies.

Results of the search

119 references were identified by electronic searches, and 27 additional records were identified by a search of clinicaltrials.gov. Most were excluded upon screening of titles and abstracts (n = 117). Full texts were consulted for the remaining 29 references, and 10 were excluded at this stage, primarily because the study was not conducted in an emergency setting (n = 7). Other reasons for exclusion at this stage were 'study population did not have asthma' (n = 2) and 'no placebo comparison' (n = 1). Several unsuccessful efforts were made to find a trial publication for one additional study (Abd El Kader 1997), which is awaiting classification. The remaining 18 citations related to 14 studies, which were included in this review. Trial flow is presented in Figure 1.

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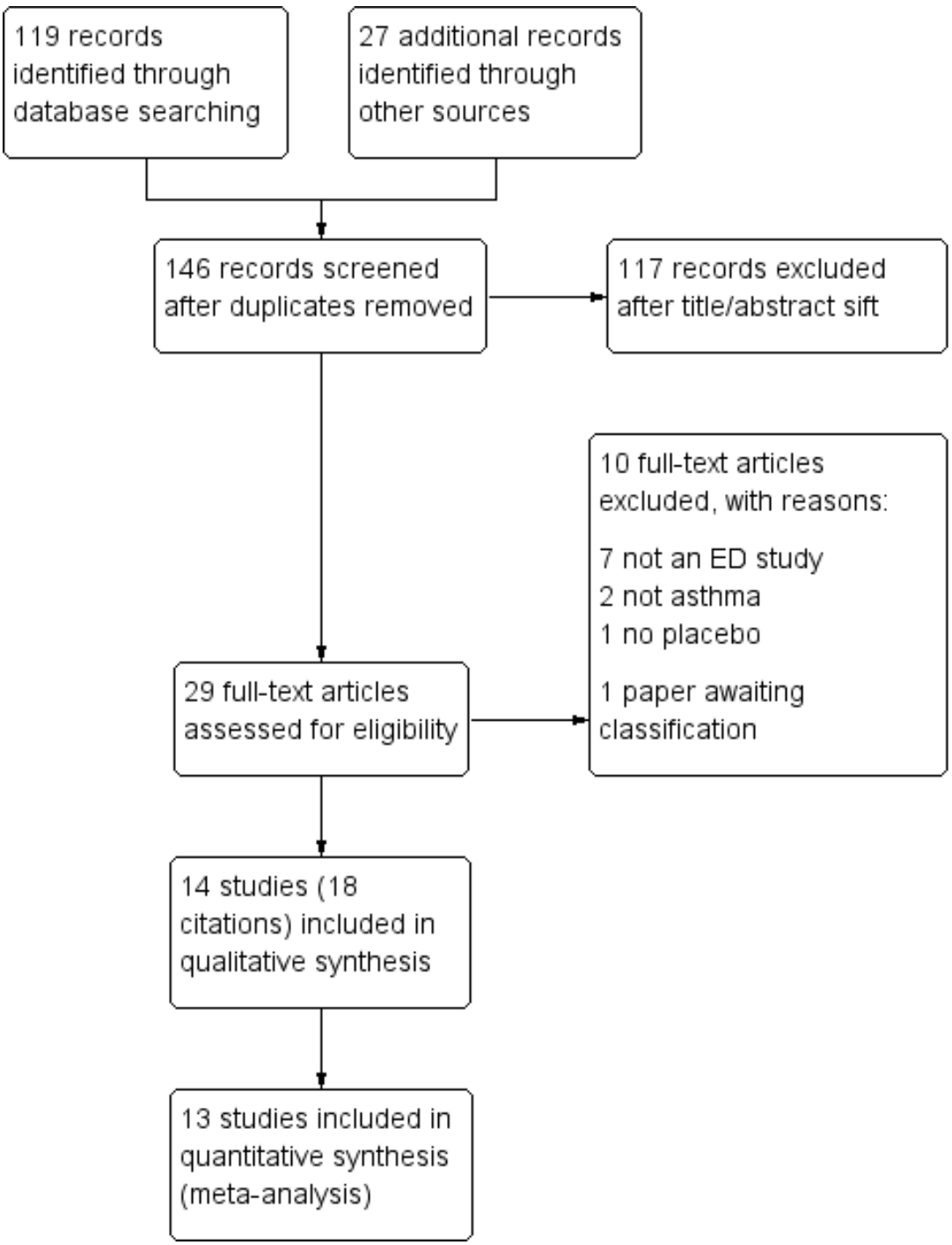
Figure 1. Study flow diagram.



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Included studies

Fourteen studies met the inclusion criteria, randomly assigning 2313 people with acute asthma to the comparisons of interest in this review. Goodacre 2013 contributed the largest sample size to the analyses, with 1109 participants randomly assigned to the two intervention groups; in contrast, Del Castillo Rueda 1991 had the smallest sample size, with 16 participants randomly assigned to the intervention groups. Mean sample size across the included studies was 165. Summary characteristics of the included trials are presented in Table 2, and full details of each included study are given in Characteristics of included studies.

Design and duration

Most of the studies included in this review were randomised, double-blinded, placebo-controlled trials. Of those that were not, two were randomised, single-blinded, placebo-controlled trials (Bilaceroglu 2001; Singh 2008), one was unblinded with the control group receiving no placebo (Green 1992) and for two trials, the study design was unclear from the information provided (Del Castillo Rueda 1991; Matusiewicz 1994). For these two studies, the former commented on randomisation but not blinding, and the latter commented on neither randomisation nor blinding, although both studies appeared to include treatment and control groups.

The duration of the studies ranged from 45 minutes (Skobeloff 1989) to 260 minutes (Tiffany 1993). Most trials reported outcome data at the end of study treatment periods, but further follow-up provided in five studies ranged from six hours to one month (Bijani 2001; Bilaceroglu 2001; Bloch 1995; Goodacre 2013; Silverman 2002). Most trials were conducted at a single centre, occurring within one ED, except for Bloch 1995, which was done across two EDs in the USA; Goodacre 2013, which took place across 34 EDs in the UK and Silverman 2002, which was completed across eight EDs in the USA.

Participant inclusion and exclusion criteria

All studies included participants with an exacerbation of asthma. However differences between studies included the measures used to define an exacerbation, with some using PEF and others using FEV_1, as well as the time at which these measurements were taken (e.g. on arrival, after initial treatment).

PEF was used in seven studies (Bijani 2001; Bilaceroglu 2001; Bradshaw 2007; Goodacre 2013; Matusiewicz 1994; Porter 2001; Skobeloff 1989). Two studies (Bijani 2001; Skobeloff 1989) used PEF < 200 L/min, Porter 2001 used PEF < 100 or < 25% predicted and Matusiewicz 1994 specified PEF < 250 L/min or < 50% predicted as the cutoff to indicate an exacerbation. Both Bilaceroglu 2001 and Goodacre 2013 specified PEF < 50% predicted as a cutoff. FEV_1 was used as a criterion for inclusion in four studies (Bilaceroglu 2001; Bloch 1995; Silverman 2002; Singh 2008), with the cutoff being FEV_1 < 75% predicted (Bilaceroglu 2001; Bloch 1995) or FEV_1 < 30% (Silverman 2002; Skobeloff 1989). Boonyavorakul 2000 used a severity score > 4 (Fischl Index, which is a composite of vital signs, PEF and clinical features). Three studies (Del Castillo Rueda 1991; Green 1992; Tiffany 1993) did not define the criteria used for an exacerbation.

Three studies did not define any exclusion criteria (Bijani 2001; Del Castillo Rueda 1991; Matusiewicz 1994). For the remaining studies (n = 11), exclusion criteria were quite consistent and included diabetes mellitus, congestive cardiac disease, hypertension, chronic renal failure, temperature > 38 °C, pneumonia, pregnancy, participants requiring ventilation and those who did not provide consent.

Baseline characteristics of participants

The most common age range used across studies was 18 to 60 years (Silverman 2002; Singh 2008; Tiffany 1993). Bloch 1995 and Green 1992 used a range of 18 to 65 years, Porter 2001 18 to 55 years and Skobeloff 1989 18 to 60 years. Two studies (Bradshaw 2007; Goodacre 2013) included participants 16 years of age and older, whilst Boonyavorakul 2000 included participants aged 15 to 65 years. Two studies included children and reported age ranges of 12 to 85 years (Bijani 2001) and six to 65 years (Bilaceroglu 2001). From the studies for which we have only the abstract, Del Castillo Rueda 1991 did not specify the age of participants, and Matusiewicz 1994 described participants as 'adults.'

Most of the studies were well matched between control and intervention with respect to sex (other than Porter 2001, in which the IV $MgSO_4$arm consisted of 50% men compared with 25% in the placebo arm).

Only four studies reported ethnicity data (Bilaceroglu 2001; Goodacre 2013; Green 1992; Silverman 2002). The percentage classified as 'white' ranged from 59% to 100% in three of these (Bilaceroglu 2001; Goodacre 2013; Green 1992), whereas Silverman 2002 had a greater preponderance of black and Hispanic participants, with only 11% to 14% of participants classified as 'white.'

Five studies distinguished smokers (Bilaceroglu 2001; Bloch 1995; Goodacre 2013; Silverman 2002; Singh 2008), and in all cases the placebo and intervention arms were well matched. The percentage of current smokers within these studies ranged from 7% to 10% in Singh 2008, to 30% to 35% in Goodacre 2013 and Silverman 2002. The remainder of the studies (Bilaceroglu 2001; Bloch 1995) combined current smokers and ex-smokers, and their proportions ranged from 29% to 50%.

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Three studies further stratified participants by severity of asthma using American (Bilaceroglu 2001; Bloch 1995) and British (Bradshaw 2007) Thoracic Society Guidelines.

As stated in the protocol, we categorised study populations on the basis of average severity to conduct a subgroup analysis. Judgements of severity were based on baseline severity characteristics presented in the trials, which are summarised in Table 3. The justification for each judgement is given in each study's characteristics table.

Characteristics of the interventions

IV $MgSO_4$

In nine studies a dose of 2 g IV was used, usually in 50 to 100 mL (250 mL in Singh 2008) of 0.9% normal saline or 5% dextrose solution, and was infused over periods ranging from 15 to 30 minutes.

Bradshaw 2007, Del Castillo Rueda 1991, Matusiewicz 1994 and Skobeloff 1989 used a dose of 1.2 g IV $MgSO_4$ in solutions akin to those mentioned above. Bijani 2001 used doses calculated by weight of 25 mg/kg; this reflects the broader age range of the participants.

Placebo group

All studies had a placebo arm except Green 1992, in which no placebo was administered to the control group. In all other cases, the same solution that was used to infuse IV $MgSO_4$ to the treatment group was used as the control solution, in equal volume and over the same time period. Boonyavorakul 2000 added 2 mL sterile water to the control solution, and Silverman 2002 does not comment on the specific solution used for control but describes it as 'like appearing solution' of equal volume.

Co-medications

A number of other drugs commonly used in acute asthma were co-administered, and there was a degree of variation in the way this was done. In all trials participants received nebulised SABA (salbutamol and, in one case, metaproterenol sulfate), and most also described the use of oxygen (n = 10) and IV corticosteroids (n = 10) before IV $MgSO_4$ was given.

Goodacre 2013 administered oral prednisolone rather than IV corticosteroids, and the form of corticosteroid administered was unclear in Bijani 2001, Del Castillo Rueda 1991 and Bilaceroglu 2001. In the latter, the decision to administer was based on the severity category to which the participant had been assigned.

Use of oxygen was described in 10 studies, although some study authors commented that this was the case only if clinically indicated (Bilaceroglu 2001; Boonyavorakul 2000). Some authors did not describe the use of oxygen, although they may not have considered this to be a drug treatment requiring mention in the treatment protocol (Bloch 1995; Del Castillo Rueda 1991; Skobeloff 1989; Tiffany 1993).

Three studies administered aminophylline or theophylline (Bijani 2001; Skobeloff 1989; Tiffany 1993), and in Skobeloff 1989, this was guided by serum theophylline levels.

Nebulised ipratropium bromide was administered in four studies (Bradshaw 2007; Goodacre 2013; Matusiewicz 1994; Singh 2008). Goodacre 2013 and Green 1992 commented that other interventions were permitted at the discretion of the treating physician, although they did not specify which ones were permitted.

Outcomes and analysis structure

Most studies reported the number of participants who required hospitalisation after treatment (n = 11), but secondary outcomes were inconsistently reported. Three studies reported length of hospital stay for those hospitalised, and only one study at high risk of bias reported the duration of ED treatment (Green 1992). Readmission was reported in Bloch 1995 and Goodacre 2013 after a week and a month, respectively.

Lung function was reported in most of the studies, although this was done in different ways (primarily percentage predicted FEV_1 and PEF, and PEF in litres per minute). Absolute values or changes in FEV_1 (L) were not consistently reported. Bloch 1995 did not report standard deviation for FEV_1, but the study was included on the basis of variance derived from the P value reported in the paper. This resulted in an unusually large standard deviation but did not significantly change the final results.

In the PEF analysis, we combined three studies reporting mean change from baseline (Bijani 2001; Skobeloff 1989; Tiffany 1993) with five reporting absolute endpoint scores (Goodacre 2013; Green 1992; Matusiewicz 1994; Porter 2001; Silverman 2002).

Four studies reported heart rate, respiratory rate and systolic blood pressure (Bloch 1995; Goodacre 2013; Silverman 2002; Singh 2008). Bijani 2001 reported respiratory rate, but the data could not be included because no measure of variance was provided. Goodacre 2013 reported oxygen saturation for participants on and off oxygen separately, but because no other studies reported data, we did not perform a meta-analysis. Partial pressure was reported in one study (Bilaceroglu 2001), but again this was not formally analysed. These results are summarised narratively.

Validated symptom scales generally were not reported in the studies, but four studies reported scores on the Borg Dyspnoea Scale (Bloch 1995; Porter 2001; Silverman 2002; Singh 2008). One additional study (Goodacre 2013) measured breathlessness using a visual analogue scale (VAS), which we chose not to analyse, as it was not validated. Boonyavorakul 2000 used the Fischl Index, which is a composite of vital signs, PEF and clinical features. As individual measures were not available, the data were not analysed.

A large degree of disparity was noted in the reporting of adverse

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events; this precluded pooling of data in the meta-analysis. Five studies reported no information on adverse events (Bijani 2001; Del Castillo Rueda 1991; Matusiewicz 1994; Silverman 2002; Tiffany 1993), although Silverman 2002 noted that no major adverse events were reported. Boonyavorakul 2000 and Green 1992 described minor adverse events such as flushing and fatigue, but these were not quantified. Other studies quantified adverse events for the duration of the treatment period, which ranged from 60 to 240 minutes. As such, we summarised information across studies narratively in the results.

Subgroup and sensitivity analyses

We conducted subgroup analyses on the primary outcome (hospital admissions) for baseline severity and co-medications. For severity, 15 groups were identified across the 11 studies reporting the outcome: two moderate, six severe and seven life threatening.

We performed the analysis based on whether ipratropium bromide was administered as described in the protocol. Bradshaw 2007, Goodacre 2013, Matusiewicz 1994 and Singh 2008 were the only studies in which ipratropium bromide was given; three of these are UK studies. However, as information about co-medications was inconsistently reported (summarised above and in Table 2), and it was often unclear when infusions or nebulisers were given, we were conservative in interpretation and have summarised the limitations of the analysis in the discussion. We could not carry out a subgroup analysis based on mean age ($\leq$ and > 65 years), as no trials solely recruited older adults.

We also conducted two sensitivity analyses excluding trials at high risk of bias for blinding and those that contributed only unpublished data. Bilaceroglu 2001, Green 1992 and Matusiewicz 1994 were removed from the prior, and only Matusiewicz 1994 from the latter. No full paper was available for Del Castillo Rueda 1991, but this study did not report hospital admissions, and although only an abstract was available in English for Bilaceroglu 2001, the full paper had been published in Turkish, from which we were able to obtain further information. None of the studies provided additional unpublished data for the primary outcome.

We added a post-hoc sensitivity analysis using change from baseline instead of endpoint means from Goodacre 2013, as baseline imbalances were noted in this study.

Excluded studies

Studies that took place outside of an acute setting were excluded, as were those concerned with the effects of nebulised magnesium sulfate (the subject of another review (Powell 2012)).

We excluded trials that were exclusively concerned with children, defined as those younger than 18 years of age. These studies will be dealt with in a separate Cochrane review (Griffiths 2014). We included studies in which participants were both older and younger than 18. Bradshaw 2007 and Goodacre 2013 included participants 16 years of age and older, and we believe that these data are applicable to adults, as we would not expect significant physiological differences between the ages of 16 and 18. Bijani 2001, Boonyavorakul 2000 and Bilaceroglu 2001 included participants 12 to 85 years and 15 to 65 years of age, respectively; we endeavoured to obtain data for adults only but were ultimately unsuccessful. Age ranges were unclear in three studies, although the implication was that participants were adults (Bilaceroglu 2001; Del Castillo Rueda 1991; Matusiewicz 1994).

Risk of bias in included studies

For details of the risk of bias rating for each study and the reasons for each rating, see Characteristics of included studies. A summary of risk of bias judgements by study and domain (allocation generation, allocation concealment, blinding and incomplete data) can be found in Figure 2.

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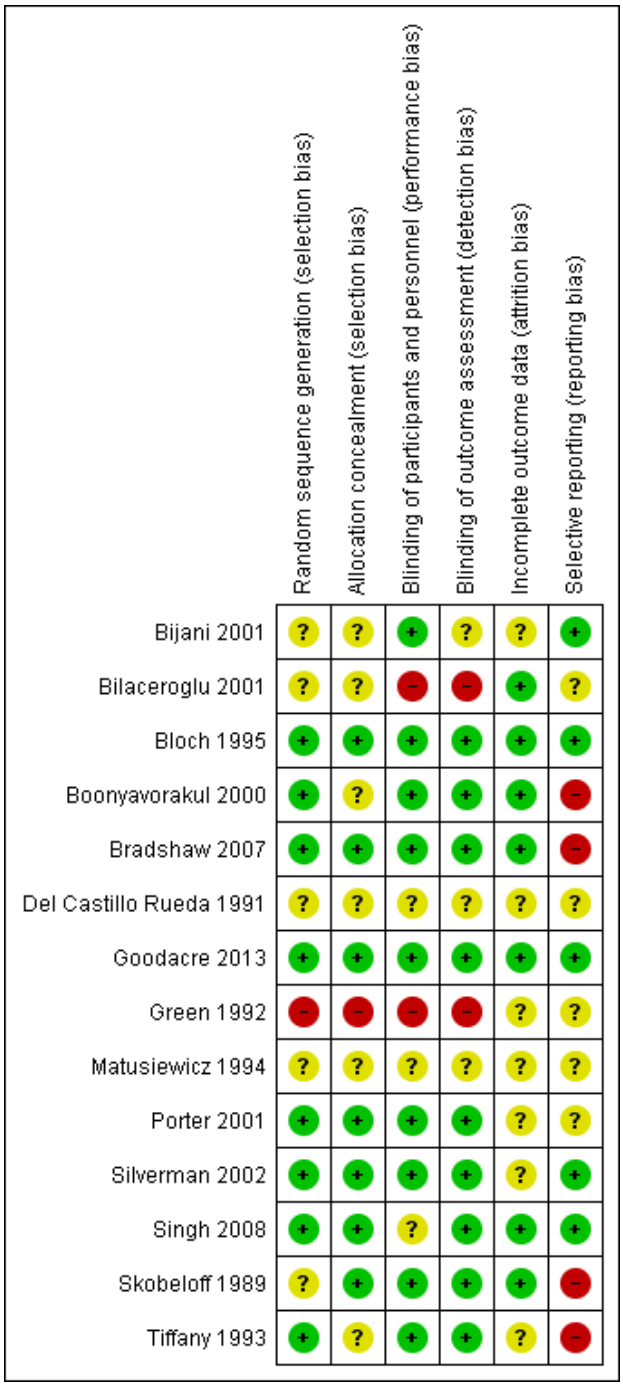
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

We assessed six studies to be at low risk of bias for random sequence generation and seven for allocation concealment. Both Bloch 1995 and Bradshaw 2007 used random number generation by pharmacy, with blinding of physicians to the allocation. Goodacre 2013 used telephone- or Internet-generated randomisation sequencing, whilst Porter 2001 used a random number generator producing a code, and in both studies, numbered treatment packs were prepared in pharmacy before they were used by physicians. Silverman 2002 used 1:1 randomisation tables, and the pharmacy prepared vials of placebo or IV $MgSO_4$ with identical appearances and labelled with study IDs. Singh 2008 used 1:1 randomisation tables, and study numbers were concealed in envelopes until allocation was completed.

Skobeloff 1989 did not provide sufficient details of random sequence allocation to warrant a low risk bias judgement but adequately described allocation concealment.

Two studies (Boonyavorakul 2000; Tiffany 1993) detailed adequate randomisation processes (computer-generated lists); in Tiffany 1993, this was managed by pharmacy, but no information about allocation concealment was provided, and hence this study was assessed to be at unclear risk in this domain.

Bilaceroglu 2001, Del Castillo Rueda 1991 and Bijani 2001 commented on randomisation, although no further details were provided and no comment on allocation concealment was made; hence these studies were assessed as unclear in both areas. The same assessment was made with Matusiewicz 1994, for which no information about randomisation or allocation concealment was provided.

We considered Green 1992 to be at high risk of bias in these domains, as participants were allocated to control or treatment group according to the day of presentation to the department.

Blinding

In the domains of both performance and detection bias, we considered most (n = 8) of the included studies to be at low risk of bias (Bloch 1995; Boonyavorakul 2000; Bradshaw 2007; Goodacre 2013; Porter 2001; Silverman 2002; Skobeloff 1989; Tiffany 1993). These were described as double-blinded placebo-controlled trials, and investigators provided adequate detail about who was blinded and commented that their primary outcomes were non-subjective assessor-rated outcomes.

Singh 2008 described this study as single-blinded; however through correspondence with the study author, we were able to ascertain that participants and assessors of spirometric and clinical outcomes were blinded, as was the chief resident who made the decision about admission. The individual administering the medication was unblinded; therefore we rated performance bias as 'unclear' and detection bias as 'low risk.'

We believe that although Bijani 2001 performed a double-blinded study with decoding done at completion of the study, limited detail was provided about who the blinded parties were, and we considered this to be unclear.

We have no information for these domains from Del Castillo Rueda 1991 and Matusiewicz 1994 and have graded them as also having unclear risk of bias.

We assessed that both Bilaceroglu 2001 and Green 1992 are at high risk of bias in these domains. The former study was single-blinded, and further correspondence with the study author confirmed that only participants were blinded to treatment, allowing for bias in assessment of outcome measures. In Green 1992, the physicians were unblinded to randomisation, and although neither participants nor respiratory therapists carrying out PEF measures were aware that a study was being conducted, they may have been aware of the treatment received.

Incomplete outcome data

We considered that in half of the included studies (n = 7), the risk of attrition bias was low, and in the other half, the risk was unclear.

In studies for which we considered the risk to be low (Bilaceroglu 2001; Bloch 1995; Boonyavorakul 2000; Bradshaw 2007; Goodacre 2013; Singh 2008; Skobeloff 1989), withdrawal rates were clearly documented and numbers were low, with similar rates reported in placebo and control groups.

In four studies (Bijani 2001; Del Castillo Rueda 1991; Matusiewicz 1994; Tiffany 1993), no information was provided about withdrawal rates, hence the reason for considering the risk to be unclear.

In Green 1992, 97 of 217 participants were excluded from analysis, with 80 participants repeat attenders (no comment on the groups to which they had been randomly assigned) and the medical records of 17 participants misplaced. No comment was made about whether there was intention to treat any of the participants who withdrew, although at the point of analysis, numbers in all groups were similar.

Porter 2001 reports that where repeat attendance to the department was documented, data from only the first presentation were used, but no further commentary was made about withdrawals.

Silverman 2002 provides a very detailed report of participants with protocol violations who were retained in the intention-to-treat data set and gives reasons for these inclusions. However, attrition rates were quite high and were not provided for each arm. As such it was unclear whether attrition was balanced between groups, and the study was rated as 'unclear.'

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Selective reporting

We considered that only five studies demonstrated low risk of bias in reporting of outcome data: Bijani 2001; Bloch 1995; Goodacre 2013; Silverman 2002; and Singh 2008. Although Bijani 2001 did not report on arterial blood gas (ABG) results as was planned, other data were well reported, and we believe that the ABG measure was not critical to the study. Both Goodacre 2013 and Singh 2008 provided further raw data when directly contacted by the review authors, and this completed the outcomes planned for assessment. The published report of Bloch 1995 provided data at only one of the prespecified time points and FEV_1 was provided graphically, but the study author provided additional data to the review authors upon request.

We considered the following studies to be unclear for risk of reporting bias: Bilaceroglu 2001; Del Castillo Rueda 1991; Green 1992; Matusiewicz 1994; and Porter 2001. We have only the abstract for both Del Castillo Rueda 1991 and Matusiewicz 1994; The former provided no outcome data, just a written description of investigator conclusions, and the latter provided outcomes at only one of the recorded time points. Bilaceroglu 2001 did provide further raw data to the review authors on request, but this still did not include all time points laid out in the methodology. Green 1992 provided outcome data, but the methodology did not indicate the primary outcome measures selected when the study was designed. Porter 2001 provided all primary outcome data at the prespecified time point; however data were also collected at other time points, and this was not reported.

We considered that four studies demonstrated high risk of reporting bias. Boonyavorakul 2000 provided only raw admission data, and severity scores were provided only in terms of 'variance.' Bradshaw 2007, Skobeloff 1989 and Tiffany 1993 provided raw data for only a subset of outcomes or time points, with remaining results presented graphically or without variance and with no reporting of raw data.

Other potential sources of bias

No additional sources of bias were identified.

Effects of interventions

See: **Summary of findings for the main comparison** IV $MgSO_4$ for treating adults with acute asthma in the emergency department

Primary outcomes

Hospital admissions

Combining 11 studies (n = 972) revealed a significant reduction in hospital admissions compared with placebo (OR 0.75, 95% CI 0.60 to 0.92; high-quality evidence; Analysis 1.1). Some heterogeneity that was not statistically significant was observed (I^2 = 28%; P value 0.18). In absolute terms, this odds ratio translates to a reduction of seven hospital admissions for every 100 adults (95% CI two to 13 fewer) treated with IV $MgSO_4$ (Figure 3). There was no reason to downgrade for any of the five domains in GRADE (risk of bias, inconsistency, indirectness, imprecision, publication bias). Specifically, risk of bias was generally low or unclear across trials, heterogeneity was not significant, trials matched the research question well, confidence intervals were relatively narrow and almost all studies contributed data to the analysis.

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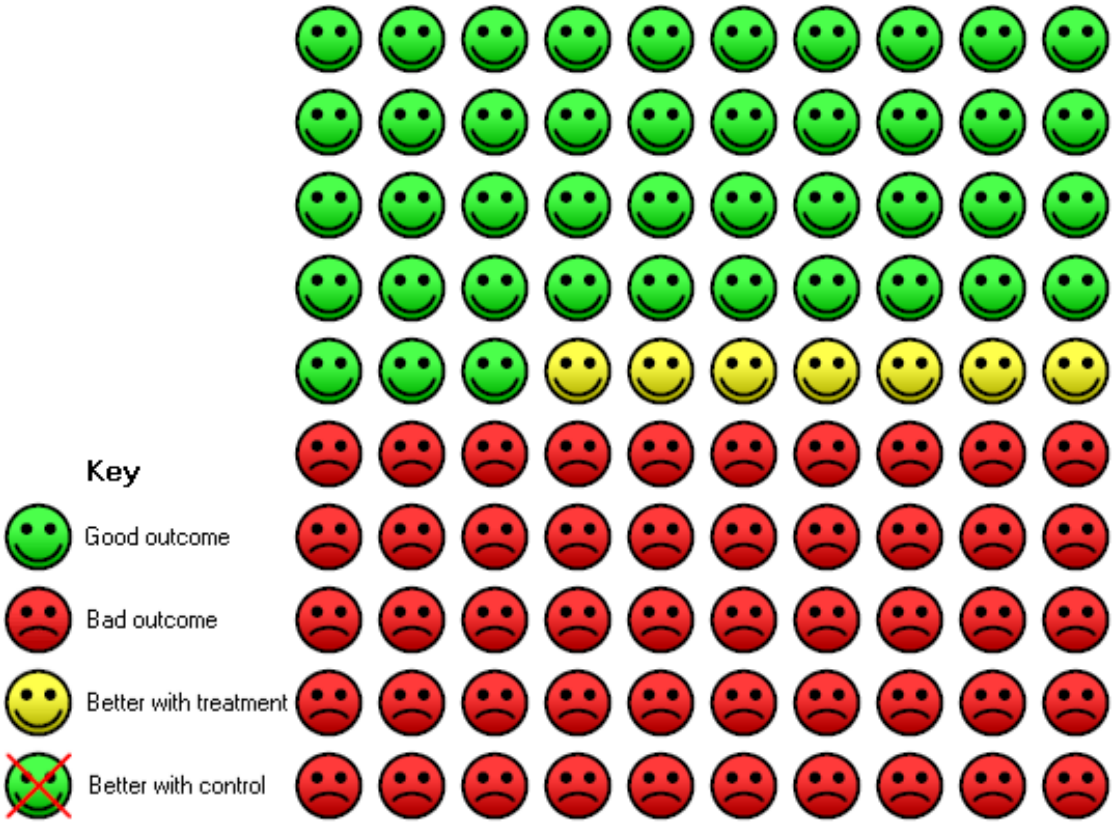
Figure 3. In the control group, 57 of 100 people were admitted to hospital, compared with 50 (95% CI 45 to 55) of 100 for the IV MgSO4 group.



Secondary outcomes

Intensive care admissions

Evidence from one study (Goodacre 2013; n = 752) showed no significant difference in admission rates between IV $MgSO_4$ and placebo (OR 2.03, 95% CI 0.70 to 5.89; moderate-quality evidence; Analysis 1.2). The same study reported the number of participants admitted to the high dependency unit and showed no significant difference between the two arms (OR 1.05, 95% CI 0.57 to 1.94; moderate-quality evidence; Analysis 1.3). Both outcomes contained few events from only one study, so they were downgraded twice for imprecision, and the quality of evidence was rated as 'low.'

ED treatment duration

Only one study (Green 1992; n = 452) reported ED treatment duration and found no significant difference between IV $MgSO_4$ and placebo (MD -4.00, 95% CI -37.02 to 29.02; low-quality evidence; Analysis 1.4). The outcome was downgraded for risk of bias and imprecision.

Length of hospital stay (days)

Combining three studies reporting the outcome (n = 949) revealed no significant difference in time spent in hospital between the IV $MgSO_4$ and placebo groups (MD -0.03, 95% CI -0.33 to 0.27; low-quality evidence; Analysis 1.5). The evidence was downgraded for risk of bias and inconsistency (I^2 = 53%; P value 0.10). As I^2 was over the 30% defined in the protocol, we performed a sensitivity analysis using random effects, which did not change the conclusions (MD -0.16, 95% CI -0.68 to 0.37).

Readmission

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Too few events were described in only two studies to indicate whether IV $MgSO_4$ had an effect on readmission to hospital compared with placebo (OR 2.30, 95% CI 0.66 to 7.99; moderate-quality evidence; Analysis 1.6). No statistical heterogeneity was noted between the studies (I^2 = 0%; P value 0.34), but the outcome was downgraded for imprecision.

Vital signs

Heart rate

Combining four studies (n = 1195) showed a small significant reduction in heart rate with IV $MgSO_4$ compared with placebo (MD -2.37, 95% CI -4.13 to -0.61; moderate-quality evidence; Analysis 1.7). However a high degree of heterogeneity was observed, which was statistically significant and warranted downgrading (I^2 = 78%; P value 0.004). A sensitivity analysis using random effects decreased precision significantly, with confidence intervals including both significant benefit and potential harm of IV $MgSO_4$ (MD -2.61, 95% CI -6.58 to 1.35).

Respiratory rate

When five studies were combined (n = 1276), IV $MgSO_4$ did not show a significant reduction in respiratory rate compared with placebo (MD -0.28, 95% CI -0.77 to 0.20; moderate-quality evidence; Analysis 1.8). Heterogeneity was not significant (I^2 = 1%; P value 0.39), but the evidence was downgraded for imprecision because confidence intervals included significant benefit and potential harm of the treatment.

Systolic blood pressure

Four studies (Bloch 1995; Bradshaw 2007; Goodacre 2013; Silverman 2002; n = 1264) reporting systolic blood pressure showed no difference between IV $MgSO_4$ and placebo (MD 0.08, 95% CI -1.89 to 2.05; moderate-quality evidence; Analysis 1.9). Heterogeneity was high, and although it was not statistically significant, authors considered it large enough to warrant downgrading for inconsistency (I^2 = 51%; P value 0.11). A sensitivity analysis using random effects did not change the conclusions (MD -0.73, 95% CI -4.13 to 2.67).

Oxygen saturations

One study reported outcomes separately for those receiving and those not receiving oxygen (Goodacre 2013). This outcome was not reported in other studies; therefore we were unable to meta-analyse the data.

Spirometry

FEV_1 (% predicted)

When four studies were combined (Bilaceroglu 2001; Bloch 1995; Silverman 2002; Singh 2008) (n = 523), significant improvement in percentage predicted FEV_1 was seen in the IV $MgSO_4$ group compared with the placebo group (MD 4.41, 95% CI 1.75 to 7.06; high-quality evidence; Analysis 1.10). No significant heterogeneity was noted among studies (I^2= 14%; P value 0.33).

During data analysis, reported standard deviations in Bilaceroglu 2001 were outliers and appeared to be more consistent with standard error values; the author confirmed that this was the case. In addition, Bloch 1995 reported no standard deviations; therefore the standard error of the mean was calculated from the graphs.

PEF (% predicted)

Three studies (Bradshaw 2007; Goodacre 2013; Silverman 2002; n = 1129) reported PEF (% predicted) and showed a statistically significant improvement in PEF with IV $MgSO_4$ compared with placebo (MD 4.78, 95% CI 2.14 to 7.43; high-quality evidence; Analysis 1.11). Heterogeneity between studies was high but was not statistically significant (I^2 = 45%; P value 0.16), so the evidence was not downgraded. A sensitivity analysis with random effects did not change our conclusions (MD 5.17, 95% CI 1.15 to 9.19). On the basis of observed baseline imbalances in the largest study (Goodacre 2013), a second sensitivity analysis using change from baseline instead of endpoint means substantially reduced the effect (MD 1.57, 95% CI -0.55 to 3.69; I^2 = 79%, P = 0.009; Analysis 2.5).

PEF (L/min)

Combining eight studies (n = 1460) revealed that IV $MgSO_4$ improved PEF compared with placebo (MD 17.40, 95% CI 8.64 to 26.17; moderate-quality evidence; Analysis 1.12). However statistically significant heterogeneity between the studies (I^2 = 50%; P value 0.05) warranted downgrading. A sensitivity analysis with random effects did not change our conclusions (MD 18.35, 95% CI 4.12 to 32.58). As with the percentage PEF predicted analysis, a second sensitivity analysis using Goodacre 2013 change from baseline substantially reduced the magnitude of effect (MD 9.44, 95% CI 2.07 to 16.81; I^2 = 68%, P = 0.003; Analysis 2.6).

Validated symptom scores

Five studies used symptom scales, all measuring breathlessness (n = 1237). The Borg Dyspnoea Scale was used by four studies (Bloch 1995; Porter 2001; Silverman 2002; Singh 2008), and Goodacre 2013 used a VAS for breathlessness. Data for the Borg Dyspnoea Scale revealed no significant change with IV $MgSO_4$ compared

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with placebo (MD -0.22, 95% CI -0.55 to 0.12; high-quality evidence; Analysis 1.13), and no significant heterogeneity between studies was noted (I^2 = 0%; P value 0.82).
Similarly, Goodacre 2013 reported no significant change in VAS score with IV $MgSO_4$ compared with placebo (MD -3.00, 95% CI -7.09 to 1.09).

Adverse events

The most commonly cited adverse events were flushing, fatigue, nausea and headache; some study authors also commented on hypotension.
Bilaceroglu 2001 reported flushing in 42% of those receiving IV $MgSO_4$ versus no flushing in the placebo group. Although paraesthesia, vertigo and hypotension were also reported, no marked differences between treatment and placebo arms were observed.
Bloch 1995 reported that 58% of those receiving IV $MgSO_4$ reported adverse events, including the sensation of flushing, fatigue and burning at the IV site, with one participant experiencing transient urticaria in the upper extremities.
Bradshaw 2007 reported minor adverse events in 8% of those receiving IV $MgSO_4$ (headache, flushing, dizziness), with only one participant in the placebo arm reporting flushing (1.5%).
Goodacre 2013 reported the rate of adverse events (death, arrhythmia, cardiac arrest, non-invasive ventilation, intubation, other) as 13% in the treatment group compared with 10% in the placebo group, although these rates fall almost entirely in the 'other' category. One death of an unspecified cause (1%) was reported in the IV $MgSO_4$ group compared with none in the placebo group. No other trials reported deaths. Goodacre 2013 reported commonly cited adverse events as a separate category and revealed a statistically significant increase in adverse events in the IV $MgSO_4$ group (OR 1.68, 95% CI 1.07 to 2.63; P value 0.025).
Both Porter 2001 and Singh 2008 reported that the difference between rates of adverse events (including deep tendon reflexes) among participants given IV $MgSO_4$ versus placebo was not statistically significant.
Skobeloff 1989 reported higher rates of fatigue (32% vs 11%), warmth (26%) and lightheadedness (5%) in the IV $MgSO_4$ group, but the numbers in this study were small.
With respect to blood pressure, Bilaceroglu 2001 reported hypotension in 5% versus 3% of participants in the treatment versus placebo groups, whilst Goodacre 2013 reported 8% versus 6%, respectively. Bradshaw 2007 reported a non-significant trend for decreasing blood pressure at 60 minutes, and Singh 2008 reported no hypotension.

Subgroup analyses

Baseline severity (moderate, severe and life-threatening exacerbations)

The test for subgroup differences revealed no statistical heterogeneity between the three severity subgroups (I^2 = 0%; P value 0.73), and between-trial heterogeneity was significant within all three subgroups (I^2 = 50%; P value 0.01).

Mean age (≤ and > 65 years)

Most studies included participants over age 65, but all population mean ages were much lower than the cutoff. As we did not have access to individual participant data within the trials, we were unable to draw any conclusions regarding potential differential effects of IV $MgSO_4$ due to age.

Co-medications (with and without nebulised ipratropium bromide)

The test for subgroup differences showed no significant differences between the four studies that administered nebulised ipratropium bromide as a co-medication and those that did not (I^2 = 0%; P value 0.82). Between-trial heterogeneity was not statistically significant within either of the two subgroups (I^2 = 28%; P value 0.18).

Sensitivity analysis

Studies at high risk of bias for blinding

When three studies that were given a 'high' or 'unclear' rating for blinding were removed (Bilaceroglu 2001; Green 1992; Matusiewicz 1994), the pooled effect for hospital admissions was slightly larger in favour of IV $MgSO_4$ (OR 0.72, 95% CI 0.57 to 0.91; Analysis 2.3). Heterogeneity was slightly larger than in the main analysis, but this difference was not statistically significant (I^2 = 35%; P value 0.15).

Unpublished data

Of the two studies for which only a conference abstract was available, one reported hospital admissions (Matusiewicz 1994). When this study was removed from the primary outcome, the magnitude of the effect in favour of IV $MgSO_4$ was slightly increased (OR 0.73, 95% CI 0.58 to 0.91), but this did not change the conclusions. Some heterogeneity that was not significant was reported (I^2 = 32%; P value 0.15).

DISCUSSION

Summary of main results

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Fourteen studies met the inclusion criteria, randomly assigning 2313 people with acute asthma to the comparisons of interest in this review. A recent large study (Goodacre 2013) accounted for a large proportion of the total number of participants (n = 752).

The included studies were mostly randomised, double-blinded trials comparing 1.2 g or 2 g IV $MgSO_4$ versus a matching placebo infusion. All of these studies included participants who had an exacerbation of asthma, although definitions and inclusion criteria varied. Ten studies included only adults; four included adults and children and were included because the mean age was over 18 years. Inclusion criteria varied, and studies assigned a level of severity to participants, which we then verified against BTS/SIGN 2012 criteria, confirming that all studies included exacerbations of at least moderate severity.

Eleven studies could be included in the primary analysis and showed that IV $MgSO_4$ reduced hospital admissions compared with placebo (OR 0.75, 95% CI 0.60 to 0.92; I^2 = 28%; P value 0.18; n = 972; high-quality evidence). In absolute terms, this odds ratio translates into a reduction of seven hospital admissions for every 100 adults (95% CI two to 13 fewer) treated with IV $MgSO_4$ (Figure 3). The test for subgroup differences did not reveal statistical heterogeneity between the three severity subgroups (I^2 = 0%; P value 0.73), or between the four studies that administered nebulised ipratropium bromide as a co-medication and those that did not (I^2 = 0%;, P value 0.82). Sensitivity analyses removing unpublished data and studies at high risk for blinding from the primary analysis did not change conclusions; this increased our confidence in the effect.

Within the secondary outcomes, evidence of high and moderate quality across three spirometric indices suggested some improvement in lung function with IV $MgSO_4$; however the clinical significance of the size of these effects is uncertain, and baseline imbalances in the largest study reduced our confidence in some of the findings. Although close, the mean difference in PEF (L/min) found in this meta-analysis did not reach the minimal clinically important difference (MCID) defined by Santanello 1999 (18.79 L/min). There are no accepted MCIDs for the percentage predicted measures reported in most of the trials. Mean FEV_1 in litres, for which an MCID does exist, was reported in only two of the 14 trials.

No difference between IV $MgSO_4$ and placebo was found for most of the non-spirometric secondary outcomes, all of which were rated of low or moderate quality (intensive care admissions, ED treatment duration, length of hospital stay, readmission, respiration rate, systolic blood pressure).

Adverse events were inconsistently reported and were not meta-analysed. The most commonly cited adverse events in the IV $MgSO_4$ groups were flushing, fatigue, nausea and headache and hypotension. However we found no significant difference in blood pressure between the IV $MgSO_4$ and placebo groups.

Overall completeness and applicability of evidence

A large degree of variation between prescribing procedures was evident in the trials, but doses used in the included studies are in accord with current BTS/SIGN 2012, GINA 2011 and NACA 2006 guidelines. However, the treatment protocols differed as to when the decision to administer IV $MgSO_4$ was made; the dosage, frequency and form of co-medications and the order in which the medications were administered in relation to one another. We suspect that differences between individual EDs both within and among countries were significant, and insufficient reporting in the trials themselves further complicated interpretation of the subgroup analysis for co-medications. As such, although no evidence suggested a difference in the efficacy of IV $MgSO_4$ delivered in settings where ipratropium bromide was prescribed, we cannot exclude the possibility that other combinations of co-medications may significantly alter the effectiveness of IV $MgSO_4$. Moreover, as almost all of the studies administered short-acting $beta_2$-agonists, oxygen and IV corticosteroids before $MgSO_4$, the evidence is suitably applied to situations for which these medications have already been prescribed. Doses of magnesium used and method and rate of delivery were relatively consistent across studies (1.2 g to 2 g via 15 to 30-minute infusion), so it is not clear whether the same effect would be observed with alternative administrations (e.g. higher dose, bolus).

The definition of hospital admission may have varied between the healthcare settings in which these studies were carried out, and this was not clearly defined in the studies. We accept that variation exists in the broader health and economic environments and in health infrastructures, such as the use of clinical decision making or observation wards, and that this is likely to have influenced the decision to admit. This variation is likely to have introduced heterogeneity in the primary outcome.

The previous version of this review (Rowe 2009) suggested the possibility of greater efficacy of treatment in more severe exacerbations; this partially informed our decision to perform a subgroup analysis based on severity. We did not find a statistically significant difference between the three severity subgroups; however, the method that we used to allocate baseline severity had limitations. We based this classification on BTS/SIGN 2012 criteria, but reporting of baseline metrics on which this guidance is based was insufficient in several studies. In studies that subdivided the population on the basis of severity (Bilaceroglu 2001; Bloch 1995; Bradshaw 2007), subgroups with a more severe condition gained greater benefit with respect to hospital admission. This suggests that within-study subgroups may serve as a more reliable way of assessing severity as an effect modifier by controlling for differences in other variables that may exist between study protocols.

We were unable to draw conclusions regarding the potential effects of age on study outcomes, as none of the studies recruited older adults. It is possible that diagnosis in this age group would be complicated by important co-morbidities (e.g. chronic obstructive

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pulmonary disease (COPD)), and that these might also affect the safety and effectiveness of IV $MgSO_4$. As such, it is likely that the conclusions of this review are not applicable to this population, or to children younger than the age of 12.

Several outcomes showed significant statistical heterogeneity among studies that was not accounted for by subgrouping results by severity of exacerbations (heart rate (HR), systolic blood pressure (BP), PEF in L/min, length of hospital stay). For HR, systolic BP and PEF in L/min, variation may be explained in part by when and how the measurement was taken, measurement error and the influence of co-medications. Length of hospital stay is highly dependent on local hospital guidelines and procedures.

We were unable to meta-analyse data related to adverse events and therefore could not draw conclusions about the safety of IV $MgSO_4$ in asthma. Some commonly cited adverse events were consistently reported among the studies; however, the methods of recording adverse events appeared unsystematic.

Quality of the evidence

We used GRADEpro software to assess the quality of all outcomes; this assessment is summarised in the text and in the Summary of findings for the main comparison. Most outcomes were not downgraded for risk of bias, and in the two cases in which this was done, the decision was related primarily to insufficient blinding. It is unclear how this may have affected results for the primary outcome (i.e. decision to admit), but a sensitivity analysis excluding studies in which blinding was insufficient or unclear showed that this bias is unlikely to have significantly affected the pooled estimate.

Several outcomes were downgraded for inconsistency, that is, statistical heterogeneity, between studies. In these cases we performed sensitivity analyses using a random-effects model, which did not alter conclusions. The clinical source of the statistical heterogeneity remains unclear in most cases, as planned subgroup analyses were performed only on the primary outcome. Most of the secondary outcomes for which heterogeneity was observed contained a small number of studies; therefore it is unlikely that subgrouping of results would have allowed a meaningful distinction between severity or co-medication subgroups.

Studies included in this review were directly relevant to our review question with respect to participants recruited, interventions and comparisons provided, healthcare setting selected, and outcome measures used, so none of the evidence was downgraded for indirectness.

Four outcomes were downgraded for imprecision on the basis of their wide confidence intervals (intensive care unit (ICU) admission, ED treatment duration, PEF in L/min, respiratory rate (RR)). In each case the review authors made a clinical judgement regarding the minimal clinically important difference in relation to the confidence intervals. Moreover, with the exception of ED treatment duration, evidence from related outcomes (e.g. other spirometric measures) helped us draw conclusions when imprecision was due to a small number of participants or events.

No outcomes were downgraded for publication bias, although several of the secondary outcomes included a small number of studies. No incidences were identified in which studies stated outcomes and failed to report them, but this was generally a result of insufficient reporting of intended outcomes and the fact that the studies could not be linked to trial registrations. Most studies were conducted before adherence to trial registration or reporting standards was common practice, so in most cases we were unable to definitively judge whether the evidence was compromised as a result of deliberate or inadvertent selective reporting.

To resolve uncertainties related to risk of bias and missing data, we made an effort to contact all study authors. We received additional data from four of these authors (Bilaceroglu 2001; Bloch 1995; Goodacre 2013; Singh 2008), were unable to obtain current contact details for two (Matusiewicz 1994; Porter 2001) and received no response from the remaining eight.

Potential biases in the review process

We made every effort to adhere to Cochrane methods during the review process. All study characteristics and numerical data were extracted by at least two review authors, and discrepancies were resolved through discussion. The same was true for risk of bias ratings, and none of the review authors have conflicting interests. We performed relatively broad searches that were screened by at least two review authors independently, and we included studies regardless of language of publication. As a result, It is unlikely that any published studies were missed during study selection. In addition, review authors attempted to contact all study authors to clarify study methodology or to obtain additional data when details were not included in the published reports. We received detailed replies and additional data from four study authors, but in most cases, it was unclear whether study authors had failed to receive the request or were simply unable to provide the information required.

The subgroup analysis based on exacerbation severity introduced the potential for internal bias, despite efforts to remove bias by consultation with an independent fourth party. Although we were transparent in the method of classification, an element of subjectivity due to reporting standards was noted in some trials; this reduced our confidence in the subgroup findings.

Agreements and disagreements with other studies or reviews

Our literature search identified five systematic reviews with meta-analyses comparing use of IV $MgSO_4$ versus placebo in adults with acute asthma (Alter 2000; Mohammed 2007; Rodrigo 2000; Rowe 2009; Shan 2013). One of these, Rowe 2009, was a previous Cochrane review, and Shan 2013, the most recent research

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synthesis, included the greatest number of trials (n = 16), 10 of which are included in this review.

The main outcomes analysed were hospital admissions and spirometric data. None of the existing reviews found a statistically significant reduction in hospital admissions across all severity subgroups. However Rowe 2009 found a significant reduction in hospital admissions within the more severe group (OR 0.10, 95% CI 0.04 to 0.27) and suggested that IV $MgSO_4$ might play a role in these more severe exacerbations. Hospital admission data for Shan 2013 were on the border of statistical significance (P value 0.06). Alter 2000 and Shan 2013 reported significant improvement in pooled spirometric measures for those receiving IV $MgSO_4$, whilst Mohammed 2007 reported weak evidence to support this (SMD 0.25, 95% CI -0.01 to 0.51; P value 0.05). Pooled analyses in Rodrigo 2000 and Rowe 2009 showed no significant improvement in lung function for those given IV $MgSO_4$.

In keeping with these reviews, we found evidence that IV $MgSO_4$ improves lung function on a variety of spirometric measures. However, our findings differ in that when all data regardless of severity criteria were pooled, a statistically significant reduction in hospital admissions was seen among those treated with IV $MgSO_4$. We did not draw firm conclusions regarding the extent to which severity of exacerbation affects the efficacy of IV $MgSO_4$ because differences in the ways the studies were conducted made it difficult to assess the effect of exacerbation severity independent of other effect moderators.

Several reasons may account for the discrepancies between our conclusions and those of previous evidence syntheses. Unlike some previous systematic reviews (Alter 2000; Mohammed 2007; Rowe 2009; Shan 2013), our inclusion criteria did not include paediatric trials. Several additional trials have been published since the previous version of this review, and this warranted synthesising of data for adults separately from data for children (Bijani 2001; Bilaceroglu 2001; Boonyavorakul 2000; Bradshaw 2007; Del Castillo Rueda 1991; Goodacre 2013; Matusiewicz 1994; Porter 2001; Singh 2008). One of these trials, Goodacre 2013, is a recent randomised controlled trial with a large sample size; it accounted for a significant proportion of the total weight in several of our analyses. Evidence for the use of IV $MgSO_4$ in the paediatric population will be analysed in a separate Cochrane review, which is currently in production. Some previous syntheses have included trials of nebulised magnesium sulfate (Mohammed 2007; Rodrigo 2000; Shan 2013), which we did not include, as this is the subject of an existing Cochrane review (Powell 2012).

AUTHORS' CONCLUSIONS

Implications for practice

This review provides evidence that a single infusion of 1.2 g or 2 g IV $MgSO_4$ over 15 to 30 minutes reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulised short-acting $beta_2$-agonists and IV corticosteroids. Differences in the ways the trials were conducted made it difficult to assess whether the severity of the exacerbation, or additional co-medications, altered the treatment effect of IV $MgSO_4$. Evidence for other measures of benefit and safety was limited.

Implications for research

Studies conducted in these populations should clearly define baseline severity parameters and systematically record adverse events. Studies recruiting participants with exacerbations of varying severity should consider subgrouping results on the basis of accepted severity classifications.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Bijani 2001

Methods	**Design**: randomised, double-blind, placebo-controlled study based in Iran. No information provided regarding location of trial or dates when it was carried out Final measurement of outcomes performed at 180 minutes with participants followed for 6 hours
Participants	**Population**: 81 participants randomly assigned to control (33) or IV $MgSO_4$ infusion (48) **Inclusion criteria**: asthmatic individuals aged 12 to 85 years with an exacerbation of asthma and a peak expiratory flow (PEF) < 200 L/min who had taken bronchodilators and corticosteroids and required assisted ventilation. All participants who did not respond to treatment during the next 6 hours selected for investigation **Exclusion criteria**: not reported
Interventions	**Control group**: 100 mL normal saline infused over 30 to 45 minutes after 6 hours of no response to standard treatment **IV $MgSO_4$ group**: 25 mg/kg in 100 mL normal saline infused over 30 to 45 minutes after 6 hours of no response to standard treatment **Co-interventions**: All participants received oxygen, nebulised oxygen, nebulised salbutamol, IV aminophylline and corticosteroids
Outcomes	PEF; breathing rate; cyanosis; diaphoresis; use of respiratory muscles; ABGs all measured at baseline
Notes	**Baseline severity of population**: life threatening (based on 31% predicted PEF, respiration rate 35 breaths per minute)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no information provided as to how this was done
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double-blind' study; IV $MgSO_4$ and normal saline in 'identical containers'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	'Double-blind' study; investigators report that 'decoding was done at the completion of the study.' However the study authors do not specifically report who was measuring outcomes

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Bijani 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawal rates provided
Selective reporting (reporting bias)	Low risk	Everything reported except ABG (but this is not a primary outcome). No protocol available. Otherwise all outcomes well reported

Bilaceroglu 2001

Methods	**Design**: Randomised, single-blind trial based in Turkey. Trial was carried out in a specialist respiratory hospital in Turkey between December 1995 and December 1996 Final measurement of outcomes performed at 210 minutes, and participants followed up for 1 week afterward
Participants	**Population**: 81 participants randomly assigned to Group 1-moderate asthma (PEF > 40%) (n = 50) or Group 2-severe asthma (PEF < 40%) (n = 31) Within Group 1, participants randomly assigned to placebo (salbutamol + placebo) (n = 27) or intervention (salbutamol + magnesium) (n = 23). Within Group 2, participants randomly assigned to placebo (salbutamol + corticosteroid + placebo) (n = 14) or intervention (salbutamol + corticosteroid + magnesium) (n = 17) **Inclusion criteria**: Asthmatic participants (defined by American Thoracic Society Criteria) aged 6 to 65 years (average age 35 years) with PEF increasing by < 50% and/or FEV_1 < 75% after a single salbutamol nebuliser (2.5 mg salbutamol in 2.5 mL saline) **Exclusion criteria**: diabetes mellitus, congestive heart failure, hypertension, chronic renal failure, fever > 38 ºC, pneumonia, under mechanical ventilation and/or having suspicion of pregnancy. Furthermore, participants with > 50% increase in PEF after beta-agonist inhalation, or with FEV_1 higher than 75% of predicted value at presentation or after inhaled beta-agonist (response to treatment)
Interventions	**Control group**: Group 1 given salbutamol + placebo (100 cc of 5% dextrose solution). Group 2 given salbutamol (2.5 mg nebulised) + corticosteroid (125 mg prednisolone) + placebo (100 cc of 5% dextrose solution). In both groups, these were given at the 30th minute of the participant's arrival **IV $MgSO_4$ group**: Group 1 given salbutamol + 2 mg IV $MgSO_4$ in 100 cc dextrose solution. Group 2 given salbutamol (2.5 mg nebulised) + corticosteroid (125 mg prednisolone) + 2 mg $MgSO_4$ in 100 cc dextrose solution. Both groups given treatment at the 30th minute of their arrival **Co-interventions**: All participants received oxygen if PaO_2 < 60mmHg
Outcomes	PEF, FEV_1 and hospitalisation, length of hospital stay; change in systolic arterial pressure; change in respiration rate; dyspnoea; blood gases; serum Mg; calcium; specific adverse events
Notes	**Baseline severity of population**: Moderate and severe groups in the trial reclassified as severe and life threatening, respectively, for consistency with other study classifications and BTS guidelines (BTS/SIGN 2012)

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Bilaceroglu 2001 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' study using 1:1 tables but no other information provided regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	'Single-blind' study. Only participants blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	'Single-blind' study. Only participants blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear withdrawal rates provided. No withdrawals described after suitable participants (n = 81) were identified for randomisation. (Data from all excluded participants (n = 218) before randomisation not used in the analysis)
Selective reporting (reporting bias)	Unclear risk	Results given for stated outcomes, but some data given only in graph format. Raw data not provided

Bloch 1995

Methods	**Design**: randomised, double-blind, placebo-controlled study based in the USA. Trial carried out in 2 EDs of a voluntary and a university hospital in the USA between August 1990 and December 1991 Final measurement of outcomes performed at 240 minutes and participants followed up for 7 days
Participants	**Population**: 149 participants randomly assigned to control (68) or IV $MgSO_4$ (67) **Inclusion criteria**: asthmatic participants aged 18 to 65 years, with an exacerbation defined as FEV_1 < 75% predicted before and after a single dose of salbutamol **Exclusion criteria**: past medical history of congestive cardiac failure, diabetes mellitus, angina or chronic kidney disease; temperature > 38 °C; pregnancy; pneumonia; requiring intubation; unable to perform spirometry; unable to consent; FEV_1 > 75% before or after single dose of salbutamol
Interventions	**Control group**: 50 mL of 0.9% normal saline given 30 minutes after entry and infused over 20 minutes **IV $MgSO_4$ group**: 2 g IV $MgSO_4$ in 50 mL 0.9% normal saline given 30 minutes after

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Bloch 1995 (*Continued*)

	entry and infused over 20 minutes **Co-interventions**: All participants received Inhaled albuterol (2.5 mg in 2.5 mL normal saline) on arrival. If FEV_1 < 40% predicted, or if participants had received oral corticosteroids within the past 6 months, they received 125 mg IV methylprednisolone within 30 minutes of presentation. Some participants were already taking theophylline before the time of presentation
Outcomes	Hospitalisation rate; FEV_1 at 2 hours after baseline; repeat hospitalisations; respiratory rate; heart rate; systolic blood pressure; Borg score; wheeze score; adverse events
Notes	Funded by the Nina Weisman Pulmonary Research Fund **Baseline severity of population**: moderate and severe groups in the trial reclassified as severe and life threatening, respectively, for consistency with other study classifications and BTS guidelines (BTS/SIGN 2012)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned by the pharmacy using 'computer-generated tables'
Allocation concealment (selection bias)	Low risk	'All physicians were blinded to the randomisation that was done by the pharmacy'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double -blind' but no description of how interventions were disguised
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No subjective assessor-rated outcomes, and the investigators remained blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported: 'Fourteen patients were excluded after randomisation.' 'Four patients were included as an intention to treat because the protocol was violated…' 'In six patients their baseline FEV1 was unavailable and these were included in the analysis as a whole and excluded from subgroup analysis' Overall small attrition numbers
Selective reporting (reporting bias)	Low risk	Published report provided data only at one of the prespecified time points; FEV1 was provided graphically, but the study author provided additional data upon request

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Boonyavorakul 2000

Methods	**Design**: randomised, double-blind, placebo-controlled study based in Thailand. Trial carried out in a single ED between March and November 1997 Final measurement of outcomes performed at 240 minutes with no further follow-up of participants
Participants	**Population**: 34 participants randomly assigned to control (16) or IV $MgSO_4$ (17) **Inclusion criteria**: asthmatic individuals aged 15 to 65 years with acute severe asthma, defined as having a severity score > 4, who consented to enter the trial **Exclusion criteria**: co-morbidities including ischaemic heart disease, hypertension, diabetes mellitus, chronic kidney disease, infection or pregnancy; or a FISCHL Index < 4
Interventions	**Control group**: 2 mL of sterile water in 50 mL 0.9% normal saline **IV $MgSO_4$ group**: 2 g of Mg SO_4 in 50 mL 0.9% normal saline **Co-interventions**: All participants received 5 mg intravenous dexamethasone, 2.5 mg nebulised salbutamol at 0, 20, 40, 60 minutes and oxygen via mask if necessary
Outcomes	Hospitalisation rate; severity score FISCHL Index at 0, 60, 120, 180, 240 minutes (comprising pulse rate, respiratory rate, PEF, dyspnoea, accessory muscle use and wheeze)
Notes	**Baseline severity of population**: life threatening (based on comparison of vital stats [HR 125 bpm, respiration rate 33] with other studies with multiple baseline measurements)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using a 'computer generated random list'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study. 'Study investigators and patients were blind to whether they administered/received $MgSO_4$ or placebo'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Only 2 physicians took responsibility for caring for patients in ED. They measured all clinical data and made the decision regarding admission. They were blinded and the protocol was not violated during the study'
Incomplete outcome data (attrition bias) All outcomes	Low risk	'One patient in the placebo group didn't consent and so was removed from the group.' Equal numbers of withdrawals from both groups (17 magnesium and 16 placebo)

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Boonyavorakul 2000 (*Continued*)

Selective reporting (reporting bias)	High risk	Incomplete reporting: only the admission data given. Severity scores given only in terms of 'variance' and no raw data provided

Bradshaw 2007

Methods	**Design**: randomised, double-blind, placebo-controlled study based in Edinburgh. Trial carried out in a teaching hospital. No information provided regarding the dates of the study Final measurement of outcomes performed at 60 minutes and no follow-up of participants reported
Participants	**Population**: 129 participants randomly assigned to control (67) or IV $MgSO_4$ (62) **Inclusion criteria**: asthmatic individuals aged 16 years and older, with asthma exacerbation defined as PEF < 75% **Exclusion criteria**: co-morbidities including chronic obstructive pulmonary disease, pneumonia, congestive cardiac failure, coronary artery disease, chronic kidney disease, hypertension or pregnancy; participants who are unable to carry out peak flow measurements
Interventions	**Control group**: 50 mL 0.9% normal saline infused over 15 minutes **IV $MgSO_4$ group**: 1.2 g IV $MgSO_4$ in 50 mL 0.9% normal saline infused over 15 minutes **Co-interventions**: All participants received 35% oxygen, 5 mg nebulised salbutamol, 500 mcg nebulised ipratropium bromide, 200 mg IV hydrocortisone
Outcomes	% predicted PEF at 60 minutes (repeated at 15, 30, 45 and 60 minutes), hospital admission rates (decision made at 60 minutes), blood pressure and pulse at 60 minutes
Notes	**Baseline severity of population**: Moderate, severe and life-threatening classifications within the trial were not changed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomised using random number generation under the control of hospital pharmacy'
Allocation concealment (selection bias)	Low risk	Randomisation done by pharmacy and physicians remained blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind, placebo controlled study'. IV $MgSO_4$ and placebo 'identical in appearance'

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Bradshaw 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	No subjective assessor-rated outcomes (3 × PEF), and the investigators remained blind. The 'decision to admit/discharge was made by the attending physician'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Well reported. 21 participants excluded prior to randomisation. None after that
Selective reporting (reporting bias)	High risk	Incomplete reporting- primary and secondary outcomes given at 60 minutes but not at other intervals (data given in graph format but no raw data available, making analysis difficult)

Del Castillo Rueda 1991

Methods	**Design**: randomised, no information on blinding, placebo-controlled study based in Spain. Trial carried out in one hospital in Madrid Information regarding duration of the trial and follow-up of participants not provided
Participants	**Population**: 16 participants randomly assigned to control (6) and IV $MgSO_4$ (10) **Inclusion criteria**: participants with acute asthma. No details provided regarding age or how acute asthma was defined **Exclusion criteria**: not reported
Interventions	**Control group**: not reported **IV $MgSO_4$ Group**: 1.2 g of IV $MgSO_4$ in physiological fluid infused over 20 minutes **Co-interventions**: All participants received corticosteroids and beta-2 agonists
Outcomes	PEF; ABG; hospitalisation rate; length of stay; adverse events
Notes	Abstract only **Baseline severity of population**: unknown, but did not contribute data to the primary analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors describe the study as 'randomised, double blind,' but no details given about the blinding process. Difficult to comment based on the abstract alone
Allocation concealment (selection bias)	Unclear risk	No information provided. Difficult to comment based on the abstract alone

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Del Castillo Rueda 1991 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided. Difficult to comment based on the abstract alone
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided. Difficult to comment based on the abstract alone
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided. Difficult to comment based on the abstract alone
Selective reporting (reporting bias)	Unclear risk	No information provided. Difficult to comment based on the abstract alone

Goodacre 2013

Methods	**Design**: randomised, double-blind, placebo-controlled study based in the UK. Trial carried out in the EDs of 34 hospitals across the UK between 30 July 2008 and 30 June 2012 Final measurement of outcomes performed at 120 minutes; however decision to admit made at 240 minutes and participants followed up for 1 month
Participants	**Population**: 1109 participants randomly assigned to control (364) and IV $MgSO_4$ (406) and one other group that was not relevant to our study (nebulised magnesium; n = 339) **Inclusion criteria**: asthmatic individuals aged 16 years and older with severe acute asthma (defined as PEF < 50%, respiratory rate > 25 breaths/min, heart rate > 110 bpm, unable to complete sentences) **Exclusion criteria**: life-threatening exacerbations, contraindications to study drugs (e. g. pregnancy, chronic kidney disease, liver failure, heart block, high serum magnesium levels), participants who are unable to consent, previous participants in the 3Mg trial, those who had received magnesium in the previous 24 hours
Interventions	**Control group**: 100 mL 0.9% normal saline infused over 20 minutes **IV $MgSO_4$ group**: 2 g $MgSO_4$ in 100 mL 0.9% normal saline infused over 20 minutes **Co-interventions**: All participants received oxygen, 5 mg nebulised salbutamol, 500 mcg nebulised ipratropium bromide and oral prednisolone during recruitment, followed by 5 mg salbutamol added to each trial nebuliser. Other treatments allowed at the discretion of the clinician
Outcomes	Hospital admissions (after ED treatment or within the next 7 days); participant breathlessness (VAS score), mortality; adverse events; use of ventilation or respiratory support
Notes	Funded by the UK National Institute for Health Research Health Technology Assessment Programme **Baseline severity of population**: We classified baseline severity as moderate, based on PEF of 433 L/min and PEF percentage predicted of 52%

Risk of bias

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Goodacre 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using telephone or Internet randomisation system managed by Sheffield Clinical Trials Research Unit
Allocation concealment (selection bias)	Low risk	'Participants were allocated to numbered treatment packs kept in the ED'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind placebo controlled study.' Numbered treatment packs used. Not clear whether these were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Participants, hospital staff and research staff were masked to allocated treatment'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Well documented: '25 withdrew without starting trial drug, were recruited in error or could not be allocated to a treatment pack'
Selective reporting (reporting bias)	Low risk	Primary outcomes well reported in the published paper, but no information provided regarding clinical data (e.g. BP, RR, HR) or participant satisfaction/QOL data (potentially reported elsewhere). However the author did supply all of this information on request

Green 1992

Methods	**Design**: prospective unblinded trial (no placebo and unclear whether randomised) based in California, USA. Trial carried out in a single ED of an urban teaching hospital between 29 March 1990 and 21 March 1991 Final measurement of outcomes time point unclear
Participants	**Population**: 137 participants allocated to IV $MgSO_4$ treatment or no IV $MgSO_4$ treatment on alternate days of the week **Inclusion criteria**: asthmatic individuals aged 18 to 65 years with an exacerbation of asthma (no further definition) **Exclusion criteria**: co-morbidities including ischaemic heart disease, hypertension, angina, congestive cardiac failure, heart block, chest pain, metastatic cancer, chronic kidney disease, temperature > 38.3 ^oC, blood pressure < 120 systolic, pregnancy, pneumonia or requiring intubation
Interventions	**Control group**: no IV $MgSO_4$ given **IV $MgSO_4$ Group**: 2 g IV $MgSO_4$ in 50 mL D5W over 20 minutes within 45 minutes of treatment initiation

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Green 1992 (*Continued*)

	Co-interventions: All participants received oxygen, 2.5 mg inhaled albuterol, 125 mg IV methylprednisolone. Other medications (e.g. theophylline, injectable beta-agonists, epinephrine) were allowed at the discretion of the attending physician
Outcomes	Hospitalisation rate; ED treatment time (for those discharged); adverse events; relapse rate; PEF change from baseline; length of hospital stay
Notes	**Baseline severity of population**: severe (based on low PEF L/min 143 and high vital stats, HR 108 and respiration rate 29)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	'Patients presenting on odd days were given magnesium and those on even days did not receive magnesium'
Allocation concealment (selection bias)	High risk	Allocation dependent on the days they presented. Unblinded and not randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	'Physicians were not blinded to patient randomisation; however, patients and respiratory therapists were unaware that a study was being performed'
Blinding of outcome assessment (detection bias) All outcomes	High risk	Respiratory therapists (who were measuring the PEF) 'were unaware that a study was going on,' but no formal blinding at all
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported as follows: 217 participants in total. 80 were repeats and so were excluded (although it is unclear from which groups these came), and 17 others were removed from data analysis because of misplaced records (total 97/217). No evidence of ITT. Final group sizes of quite equal size: 58 and 62
Selective reporting (reporting bias)	Unclear risk	All outcome data given but not clearly described as primary or secondary outcomes in the initial methodology

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Matusiewicz 1994

Methods	**Design**: unclear. Based in Scotland but unclear as to location where the trial was carried out and during what dates Final measurement of outcomes performed at 60 minutes and information about follow-up of participants not provided
Participants	**Population**: 131 participants allocated to control (67) or IV $MgSO_4$ (64) **Inclusion criteria**: Adults (age not specified) with acute severe asthma (defined as PEF < 250 or 50% of best previous PEF) **Exclusion criteria**: not reported
Interventions	**Control group**: 50 mL 0.9% normal saline infused over 15 minutes **IV $MgSO_4$ group**: 1.2 mg IV $MgSO_4$ in 50 mL 0.9% normal saline infused over 15 minutes **Co-interventions**: All participants received 5 mg nebulised salbutamol, 500 mcg nebulised ipratropium bromide, oxygen, 200 mg IV hydrocortisone. Aminophylline was given at the discretion of the attending physician
Outcomes	PEF at 15, 30, 45, 60 minutes; hospitalisation rate
Notes	**Baseline severity of population**: We have classified this population as severe based on inclusion criteria of PEF < 250 L/min and < 50% predicted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Difficult to comment based on the abstract alone
Allocation concealment (selection bias)	Unclear risk	No information provided. Difficult to comment based on the abstract alone
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	'Double blind placebo controlled parallel group study.' No mention of randomisation nor details of blinding. Difficult to comment based on the abstract alone
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided. Difficult to comment based on the abstract alone
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided. Difficult to comment based on the abstract alone
Selective reporting (reporting bias)	Unclear risk	No information provided. Difficult to comment based on the abstract alone

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Porter 2001

Methods	**Design**: randomised, double-blind, placebo-controlled trial based in Philadelphia, USA. Trial carried out in a single urban ED, the dates of which are not specified Final measurement of outcomes performed at 60 minutes with no follow-up of participants
Participants	**Population**: 42 participants randomly assigned to control (24) and IV $MgSO_4$ (18) **Inclusion criteria**: asthmatic individuals aged 18 to 55 years with an exacerbation (defined as PEF < 100 or < 25% predicted) and able to consent **Exclusion criteria**: co-morbidities including pneumonia, chronic kidney disease, congestive cardiac failure, previous myocardial infarction, hypertension, pregnancy or possibly requiring intubation
Interventions	**Control group**: 50 mL 0.9% normal saline given immediately **IV $MgSO_4$ group**: 2 g $MgSO_4$ in 50 mL 0.9% normal saline given immediately **Co-interventions**: All participants received 2.5 mg nebulised albuterol sulfate, 125 mg IV methylprednisolone, oxygen and repeated albuterol every 20, 40 and 60 minutes
Outcomes	PEF (at 60 minutes), hospitalisation rate; Borg score; adverse effects of hypotension and hyporeflexia
Notes	**Baseline severity of population**: life threatening (based on PEF 88.5 L/min and high vital stats HR 110 and respiration rate 31)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomised using a random number generator which assigned the code'
Allocation concealment (selection bias)	Low risk	'Enrolment packs containing data recording sheets and study solutions in random order were prepared by the Pharmacy.' Saline and magnesium identical in appearance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind' study. 'Investigators, other caretakers and patients were unaware of contents of the study solution'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Investigators, other caretakers and patients were unaware of contents of the study solution'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition data specifically reported. Comment that the same participant presenting more than once was not used, indicating that investigators always used the first presentation for analysis

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Porter 2001 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Primary outcomes reported as stated at T = 60. However incomplete reporting for other time points

Silverman 2002

Methods	**Design**: randomised, double-blind, placebo-controlled study based in the United States of America (USA). Trial carried out in the EDs of eight hospitals in the USA, but dates during which this occurred not reported Final measurement of outcomes performed at 240 minutes and participants followed up for seven days
Participants	**Population**: 248 participants randomly assigned to control (126) and IV $MgSO_4$ (122) **Inclusion criteria**: asthmatic individuals aged 18 to 60 years with an exacerbation (defined as FEV_1 < 30%) who were able to stay for 4 hours and consented to being involved in the trial **Exclusion criteria**: co-morbidities such as chronic obstructive pulmonary disease or other chronic lung disease, pneumonia, temperature > 38.9 ºC, congestive cardiac failure, coronary artery disease, diabetes mellitus, chronic kidney disease, hypertension, pregnancy, requiring intubation or unable to do spirometry
Interventions	**Control group**: 50 mL 'like appearing solution' infused over 10 to 15 minutes and given at 30 minutes **IV $MgSO_4$ group**: 2 g IV $MgSO_4$ in 50 mL 0.9% normal saline infused over 10 to 15 minutes and given at 30 minutes **Co-interventions**: All participants received 2.5 mg nebulised 0.5% albuterol with 100% oxygen, 125 mg IV methylprednisolone. Albuterol subsequently given at 30, 60, 120 and 180 minutes
Outcomes	FEV_1 (at 240 minutes), hospitalisation rate; relapse rate; vital signs; Borg scale; PEF (all at 30 and 240 minutes)
Notes	Funded in part by the Max and Victoria Dreyfus Foundation **Baseline severity of population**: life threatening (based on PEF 27% predicted, FEV_1 23% predicted)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned using a 1:1 ratio randomisation table unique for each centre
Allocation concealment (selection bias)	Low risk	'Study pharmacists placed drug or placebo in identically appearing vials, with only the study ID on the label'

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Silverman 2002 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind, placebo-controlled'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators blinded ('FEV_1 results were reviewed blindly by the 2 investigators')
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Well-documented attrition rate n = 70 (28%); these 'were retained in the intention to treat data set.' However data for individual arms not given
Selective reporting (reporting bias)	Low risk	All outcome data given

Singh 2008

Methods	**Design**: randomised, single-blinded, placebo-controlled trial based in Delhi, India. Trial carried out in a single ED at the Chest Institute Final measurement of outcomes performed at 180 minutes with no further participant follow-up
Participants	**Population**: 70 participants of South Asian origin randomly assigned to control (30) and IV $MgSO_4$ (30) **Inclusion criteria**: asthmatic individuals aged 18 to 60 years with a severe exacerbation (as defined by GINA) and an FEV < 30% predicted on presentation, who were able to remain in the department for 3 hours **Exclusion criteria**: co-morbidities such as chronic obstructive pulmonary disorder (COPD) or other chronic lung disease, cardiac, renal or hepatic dysfunction, pregnancy or lactating or requiring intubation or unable to do spirometry
Interventions	**Control group**: 250 mL 0.9% normal saline infused over 20 minutes at 30 minutes **IV $MgSO_4$ group**: 2 g IV $MgSO_4$ in 250 mL 0.9% normal saline infused over 20 minutes at 30 minutes **Co-interventions**: All participants received 100 mg IV hydrocortisone on arrival (0 minutes). They then received a nebulising solution consisting of: 2.5 mg nebulised salbutamol, 1.5 mL ipratropium bromide and 2.5 mL normal saline with 100% oxygen at 0, 20 and 40 minutes
Outcomes	Change in FEV_1 % predicted, hospitalisation rate; cyanosis; stats; vital signs; Borg score
Notes	Trial done as part of an MD dissertation project funded by a grant from University of Delhi, India **Baseline severity of population**: life threatening (based on PEF 22% predicted, FEV_1 38% predicted, and high HR 127 bpm)
Risk of bias	

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Singh 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using a 1:1 ration randomisation table
Allocation concealment (selection bias)	Low risk	Random number tables used. 'Individual random numbers were kept in separate envelopes so the concealment could be maintained until the patient was included in the assigned group.' Placebo described only as 'like appearing placebo'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as a 'single blind study.' However further information from the study author confirmed that participants and assessors of spirometric and clinical outcomes were blinded to the treatment given, and the decision to admit was made by chief residents blinded to type of treatment given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study authors do not specify in the published paper who does the spirometry and clinical examination of the respiratory system at each time interval, but further information from the study authors confirms that participants and assessors of spirometric and clinical outcomes were blinded to the treatment given Decision to hospitalise or discharge was made by ED staff blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	This is clearly given for both groups (5 in each group), so it is equal, and total withdrawal percentage is low at 14%
Selective reporting (reporting bias)	Low risk	Good reporting of primary outcomes at all time points for FEV1 and at 120 minutes for Borg scale and clinical indicators

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Skobeloff 1989

Methods	**Design**: randomised, double-blind, placebo-controlled study based in Philadelphia, USA. Trial carried out in a single ED between August 1987 and February 1988 Final measurement of outcomes performed at 45 minutes, with the decision to admit at 240 minutes and no reported follow-up of participants
Participants	**Population**: 38 participants randomly assigned to control (19) and IV $MgSO_4$ (19) **Inclusion criteria**: asthmatic individuals aged 18 to 70 years with an exacerbation (initial PEF < 200 L/min) and defined as poor responders to initial treatment **Exclusion criteria**: initial PEF > 200 L/min, rectal temperature > 38 ºC, systolic blood pressure < 120, history of kidney disease, pregnancy, purulent sputum or infiltrate on chest
Interventions	**Control group**: 50 mL 0.9% normal saline infused over 20 minutes **IV $MgSO_4$ group**: 1.2 g IV $MgSO_4$ in 50 mL of 0.9% normal saline infused over 20 minutes **Co-interventions**: All participants received nebulised metaproterenol sulphate 0.3 mL in 3.0 mL of saline or albuterol sulphate 0.5 mL in 2.5 mL of saline at the discretion of the physician, 125 mg IV methylprednisolone sodium succinate and a loading dose of theophylline based on participant levels. This was followed by a maintenance infusion of 0.5 mg/kg/h. 45 to 60 minutes after initial treatment, a second nebulised treatment was given
Outcomes	PEF; hospitalisation rate; heart rate; respiration rate; mean arterial pressure
Notes	**Baseline severity of population**: severe, based on estimates from baseline characteristics graphs (HR ~ 100 bpm, RR ~ 28 rpm, PEF ~ 150 L/min)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Coded from a randomised list'
Allocation concealment (selection bias)	Low risk	Placebo/magnesium solutions prepackaged in identical vials by the pharmacy and coded from a randomised list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, randomised, placebo-controlled trial. Solutions 'prepackaged in identical vials'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded. 'The decision to admit or discharge was made by the physician caring for the patient and not influenced by the investigator'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals few and well commented on (2/14 excluded)

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Skobeloff 1989 (*Continued*)

Selective reporting (reporting bias)	High risk	All predetermined outcomes reported (except deep tendon reflexes, but the relevance of this is uncertain). However raw data not provided. Only graphs for some outcomes

Tiffany 1993

Methods	**Design**: randomised, double-blind, placebo-controlled based in Detroit, USA. Trial carried out in a single ED, the dates of which are not provided Final measurement of outcomes performed at 260 minutes with no reported follow-up of participants
Participants	**Population**: 48 participants randomly assigned to control (21) and IV $MgSO_4$ (15), and one other group that was not relevant to this review (continuous IV $MgSO_4$ infusion n = 12) **Inclusion criteria**: asthmatic individuals aged 18 to 60 years with an exacerbation who have consented to being involved in the trial **Exclusion criteria**: first episode of wheeze, history of chronic lung disease, temperature > 38.2 ºC, chronic kidney disease, congestive cardiac failure, requiring intubation and initial PEF > 200 L/min
Interventions	**Control group**: 2 g stat of 0.9% normal saline over 20 minutes followed by a placebo infusion over 4 hours **IV $MgSO_4$ group**: 2 g IV $MgSO_4$ in 0.9% normal saline over 20 minutes followed by placebo infusion over 4 hours **Co-interventions**: All participants received 2.5 mg nebulised albuterol 30 minutes apart, 125 mg IV methylprednisolone, followed by a third albuterol aerosol treatment and an aminophylline loading dose and infusion to keep levels at 15 mg/L
Outcomes	PEF and FEV_1
Notes	**Baseline severity of population**: life threatening (based on PEF L/min 115, and FEV_1 0.95 L)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned using a 'computerised random number generation under the control of the hospital pharmacy'
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind, placebo controlled study.' 'Investigators and patients were blinded to patient assignment to the study groups'

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Blinding of outcome assessment (detection bias) All outcomes	Low risk	Best of 3 PEF and FEV1 values measured (objective measurements). 'Clinical decision making (i.e. decision to admit) was left to attending physicians'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	High risk	Incomplete and no raw data reported. Results given only as variances and graphs

ABGs: Arterial blood gases; BP: Blood pressure; BTS: British Thoracic Society; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; FEV_1: Forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; HR: Heart rate; ITT: Intent-to-treat; IV: Intravenous; Mg: Magnesium; $MgSO_4$: Magnesium sulfate; PaO_2: Partial pressure of oxygen in arterial blood; PEF: Peak expiratory flow; RR: Respiratory rate; VAS: Visual analogue scale.

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

Study	Reason for exclusion
Abreu-Gonzalez 2002	Not an ED study. Design did not match inclusion criteria, laboratory study
Brunner 1985	Not an ED study. Design did not match inclusion criteria, laboratory study ('each subject serving as his own control')
Cairns 1996a	Not an ED study. Design did not match inclusion criteria, laboratory study
Harmanci 1996	Nebulised versus IV $MgSO_4$. Does not appear to have a placebo arm
Hill 1996	Not an ED study. Design did not match inclusion criteria, laboratory study
Liang 1998	No diagnosis of asthma. Child study
Okayama 1987	Not an ED study. Portion of the sample inpatients
Rolla 1988	Not an ED study. Design did not match inclusion criteria and non-emergency patients
Rolla 1994	Not an ED study
Schenk 2001	No diagnosis of asthma

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Characteristics of studies awaiting assessment *[ordered by study ID]*

Abd El Kader 1997

Methods	'Comparative study'
Participants	Patients with bronchial asthma
Interventions	Salbutamol, ipratropium bromide and magnesium sulfate
Outcomes	Ventilatory, cardiovascular and metabolic responses
Notes	Numerous attempts made to locate the paper, but no library holdings found

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DATA AND ANALYSES

Comparison 1. IV $MgSO_4$ versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admissions	11	1769	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.92]
2 Intensive care unit (ICU) admissions	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 High dependency unit (HDU) admissions	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 ED treatment duration (minutes)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Length of hospital stay (days)	3	949	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.33, 0.27]
6 Readmission	2	887	Odds Ratio (M-H, Fixed, 95% CI)	2.30 [0.66, 7.99]
7 Heart rate (bpm)	4	1195	Mean Difference (IV, Fixed, 95% CI)	-2.37 [-4.13, -0.61]
8 Respiratory rate (breaths/min)	4	1195	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.77, 0.20]
9 Systolic blood pressure (mmHg)	4	1264	Mean Difference (IV, Fixed, 95% CI)	0.08 [-1.89, 2.05]
10 FEV_1 (% predicted)	4	523	Mean Difference (IV, Fixed, 95% CI)	4.41 [1.75, 7.06]
11 PEF (% predicted)	3	1129	Mean Difference (IV, Fixed, 95% CI)	4.78 [2.14, 7.43]
12 PEF (L/min)	8	1460	Mean Difference (IV, Fixed, 95% CI)	17.40 [8.64, 26.17]
13 Borg Dyspnoea Scale score	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 2. IV $MgSO_4$ versus placebo (subgroup and sensitivity analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admissions (by severity)	11	1743	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.62, 0.95]
1.1 Moderate	2	791	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.04]
1.2 Severe	6	474	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.31]
1.3 Life threatening	7	478	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.46, 1.03]
2 Hospital admissions (by co-medications)	11	1769	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.92]
2.1 Nebulised ipratropium bromide	4	1072	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.96]
2.2 No nebulised ipratropium bromide	7	697	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.55, 1.06]
3 Hospital admissions (risk of bias sensitivity)	8	1437	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.91]
4 Hospital admissions (unpublished sensitivity)	10	1638	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.58, 0.91]
5 PEF % predicted (Goodacre change score sensitivity)	3	1129	Mean Difference (IV, Fixed, 95% CI)	1.57 [-0.55, 3.69]

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6 PEF L/min (Goodacre change score sensitivity)	8	1460	Mean Difference (IV, Fixed, 95% CI)	9.44 [2.07, 16.81]

Analysis 1.1. Comparison 1 IV MgSO4 versus placebo, Outcome 1 Hospital admissions.

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 1 Hospital admissions

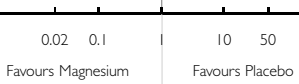
Study or subgroup	Magnesium n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bilaceroglu 2001	10/40	17/41		6.3 %	0.47 [0.18, 1.21]
Bloch 1995	17/67	24/68		8.9 %	0.62 [0.30, 1.31]
Boonyavorakul 2000	3/17	4/16		1.7 %	0.64 [0.12, 3.46]
Bradshaw 2007	49/62	52/67		5.3 %	1.09 [0.47, 2.52]
Goodacre 2013	279/394	278/358		42.6 %	0.70 [0.50, 0.97]
Green 1992	13/58	11/62		4.1 %	1.34 [0.55, 3.29]
Matusiewicz 1994	45/64	47/67		6.8 %	1.01 [0.48, 2.13]
Porter 2001	5/18	5/24		1.6 %	1.46 [0.35, 6.08]
Silverman 2002	39/122	41/126		13.8 %	0.97 [0.57, 1.66]
Singh 2008	2/30	9/30		4.2 %	0.17 [0.03, 0.85]
Skobeloff 1989	7/19	15/19		4.7 %	0.16 [0.04, 0.66]
Total (95% CI)	**891**	**878**		**100.0 %**	**0.75 [0.60, 0.92]**

Total events: 469 (Magnesium), 503 (Placebo)

Heterogeneity: Chi^2 = 13.93, df = 10 (P = 0.18); I^2 =28%

Test for overall effect: Z = 2.72 (P = 0.0066)

Test for subgroup differences: Not applicable



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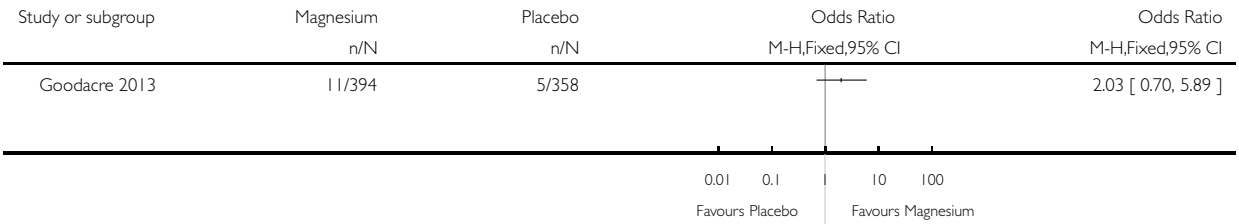
Analysis 1.2. Comparison 1 IV MgSO4 versus placebo, Outcome 2 Intensive care unit (ICU) admissions.

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 2 Intensive care unit (ICU) admissions

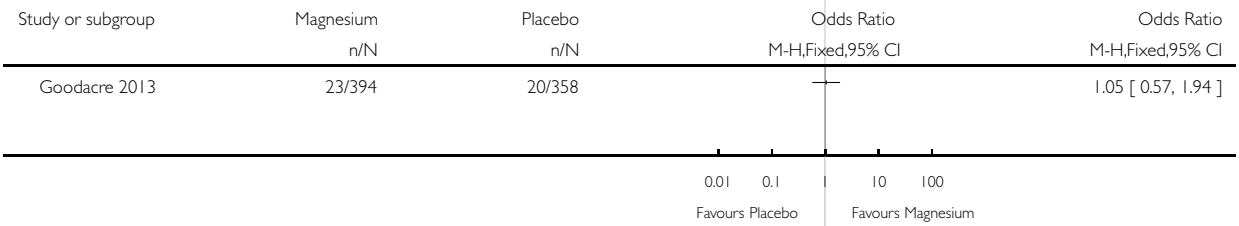


Analysis 1.3. Comparison 1 IV MgSO4 versus placebo, Outcome 3 High dependency unit (HDU) admissions.

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 3 High dependency unit (HDU) admissions



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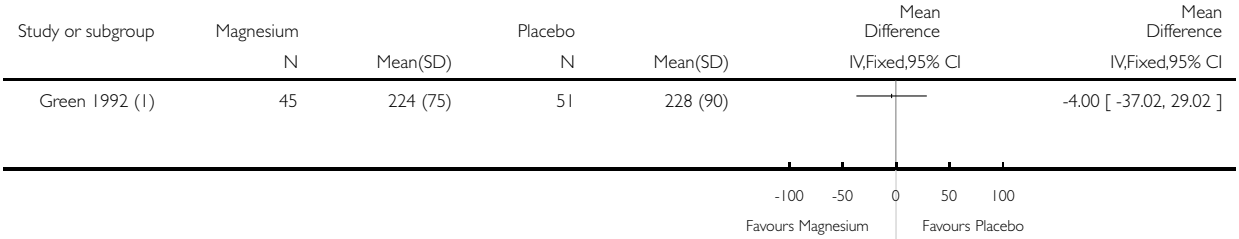
Analysis 1.4. Comparison 1 IV MgSO4 versus placebo, Outcome 4 ED treatment duration (minutes).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 4 ED treatment duration (minutes)



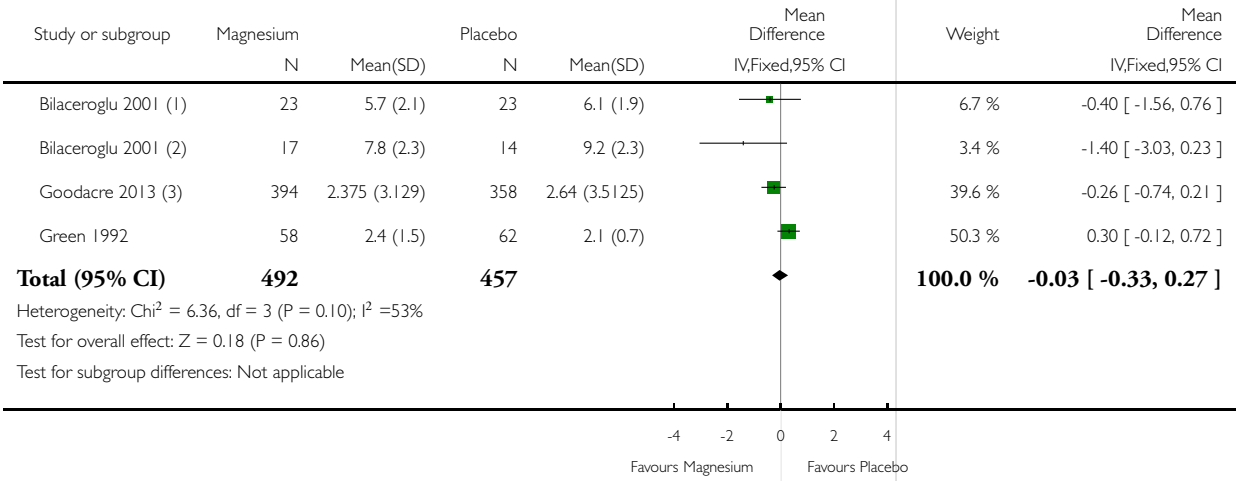
(1) Reported only for those who were discharged (i.e. those not counted in hospital admissions)

Analysis 1.5. Comparison 1 IV MgSO4 versus placebo, Outcome 5 Length of hospital stay (days).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 5 Length of hospital stay (days)



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(1) moderate

(2) severe

(3) Converted from hours to days

Analysis 1.6. Comparison 1 IV MgSO4 versus placebo, Outcome 6 Readmission.

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 6 Readmission

Study or subgroup	Magnesium n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bloch 1995 (1)	3/67	0/68		13.2 %	7.43 [0.38, 146.75]
Goodacre 2013 (2)	5/394	3/358		86.8 %	1.52 [0.36, 6.41]
Total (95% CI)	**461**	**426**		**100.0 %**	**2.30 [0.66, 7.99]**

Total events: 8 (Magnesium), 3 (Placebo)

Heterogeneity: $Chi^2 = 0.91$, df = 1 (P = 0.34); $I^2 = 0.0\%$

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable

(1) within 1 week

(2) within 1 month

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Analysis 1.7. Comparison 1 IV MgSO4 versus placebo, Outcome 7 Heart rate (bpm).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 7 Heart rate (bpm)

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bloch 1995 (1)	67	102.5 (15.7)	68	99.9 (16.3)		10.6 %	2.60 [-2.80, 8.00]
Goodacre 2013 (2)	394	105.7 (18.1)	358	105.9 (17.5)		47.8 %	-0.20 [-2.75, 2.35]
Silverman 2002 (3)	122	96 (15)	126	102 (15)		22.2 %	-6.00 [-9.73, -2.27]
Singh 2008 (4)	30	100 (7.43)	30	106.27 (8.34)		19.4 %	-6.27 [-10.27, -2.27]
Total (95% CI)	**613**		**582**			**100.0 %**	**-2.37 [-4.13, -0.61]**

Heterogeneity: Chi^2 = 13.33, df = 3 (P = 0.004); I^2 =78%

Test for overall effect: Z = 2.64 (P = 0.0084)

Test for subgroup differences: Not applicable

(1) All groups

(2) at 120 mins

(3) at 240 mins

(4) at 120 mins

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Analysis 1.8. Comparison 1 IV MgSO4 versus placebo, Outcome 8 Respiratory rate (breaths/min).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 8 Respiratory rate (breaths/min)

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bloch 1995 (1)	67	18.9 (3.1)	68	20 (4.1)		15.7 %	-1.10 [-2.32, 0.12]
Goodacre 2013 (2)	394	20.6 (5.3)	358	21 (5.4)		40.1 %	-0.40 [-1.17, 0.37]
Silverman 2002 (3)	122	20 (4.1)	126	20 (4.1)		22.6 %	0.0 [-1.02, 1.02]
Singh 2008 (4)	30	21.83 (1.55)	30	21.6 (2.46)		21.7 %	0.23 [-0.81, 1.27]
Total (95% CI)	**613**		**582**			**100.0 %**	**-0.28 [-0.77, 0.20]**

Heterogeneity: Chi^2 = 3.03, df = 3 (P = 0.39); I^2 =1%

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

(1) All groups at 120 mins

(2) at 120 mins

(3) at 240 mins

(4) at 120 mins

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Analysis 1.9. Comparison 1 IV MgSO4 versus placebo, Outcome 9 Systolic blood pressure (mmHg).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 9 Systolic blood pressure (mmHg)

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bloch 1995 (1)	67	122.7 (17.4)	68	126 (15.6)		12.5 %	-3.30 [-8.88, 2.28]
Bradshaw 2007 (2)	62	123.5 (33)	67	134.6 (33)		3.0 %	-11.10 [-22.50, 0.30]
Goodacre 2013 (3)	394	125.5 (16.5)	358	124.9 (18.5)		61.6 %	0.60 [-1.92, 3.12]
Silverman 2002 (4)	122	123 (18)	126	121 (15)		22.8 %	2.00 [-2.13, 6.13]
Total (95% CI)	**645**		**619**			**100.0 %**	**0.08 [-1.89, 2.05]**

Heterogeneity: Chi^2 = 6.10, df = 3 (P = 0.11); I^2 =51%

Test for overall effect: Z = 0.08 (P = 0.94)

Test for subgroup differences: Not applicable

(1) All groups at 120 mins

(2) All groups at 60 mins. SD estimated from p value.

(3) at 120 mins

(4) at 240 mins

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Analysis 1.10. Comparison 1 IV MgSO4 versus placebo, Outcome 10 FEV1 (% predicted).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 10 FEV_1 (% predicted)

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bilaceroglu 2001 (1)	23	56.8 (19.2313)	23	57.15 (17.6007)		6.2 %	-0.35 [-11.00, 10.30]
Bilaceroglu 2001 (2)	17	62.34 (16.245)	17	52.66 (16.6161)		5.8 %	9.68 [-1.37, 20.73]
Bloch 1995 (3)	67	55 (20.4634)	68	56 (20.6155)		14.7 %	-1.00 [-7.93, 5.93]
Silverman 2002 (4)	122	48.2 (18.1)	126	43.5 (18.7)		33.6 %	4.70 [0.12, 9.28]
Singh 2008 (5)	30	62.84 (10.02)	30	56.7 (6.2)		39.7 %	6.14 [1.92, 10.36]
Total (95% CI)	**259**		**264**			**100.0 %**	**4.41 [1.75, 7.06]**

Heterogeneity: Chi^2 = 4.64, df = 4 (P = 0.33); I^2 =14%

Test for overall effect: Z = 3.25 (P = 0.0011)

Test for subgroup differences: Not applicable

(1) Moderate at 180 mins

(2) Severe at 180 mins

(3) All groups at 120 mins. SEM calculated from graph.

(4) at 240 mins

(5) at 120 mins

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Analysis 1.11. Comparison 1 IV MgSO4 versus placebo, Outcome 11 PEF (% predicted).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 11 PEF (% predicted)

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bradshaw 2007 (1)	62	65.4 (21.0197)	67	62.8 (21.0197)		13.3 %	2.60 [-4.66, 9.86]
Goodacre 2013 (2)	394	68.6 (23.3)	358	65 (22.7)		64.7 %	3.60 [0.31, 6.89]
Silverman 2002 (3)	122	62.7 (24.3)	126	53.1 (20.9)		22.0 %	9.60 [3.95, 15.25]
Total (95% CI)	**578**		**551**			**100.0 %**	**4.78 [2.14, 7.43]**

Heterogeneity: Chi^2 = 3.64, df = 2 (P = 0.16); I^2 =45%

Test for overall effect: Z = 3.54 (P = 0.00040)

Test for subgroup differences: Not applicable

(1) All groups at 60 mins

(2) at 120 mins

(3) at 240 mins

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Analysis 1.12. Comparison 1 IV MgSO4 versus placebo, Outcome 12 PEF (L/min).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

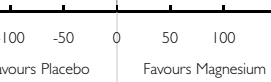
Outcome: 12 PEF (L/min)

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bijani 2001 (1)	48	82.6 (40.1836)	33	47.8 (49.9777)		18.3 %	34.80 [14.31, 55.29]
Goodacre 2013 (2)	394	288.1 (111.2)	358	278.9 (105.5)		32.0 %	9.20 [-6.29, 24.69]
Green 1992 (3)	58	263 (122)	62	278 (104)		4.6 %	-15.00 [-55.69, 25.69]
Matusiewicz 1994 (4)	64	279 (112)	67	256 (106.4096)		5.5 %	23.00 [-14.45, 60.45]
Porter 2001 (5)	18	211 (104)	24	252 (108)		1.8 %	-41.00 [-105.62, 23.62]
Silverman 2002 (6)	122	272 (144)	126	236 (123)		6.9 %	36.00 [2.62, 69.38]
Skobeloff 1989 (7)	19	72 (80)	19	8 (80)		3.0 %	64.00 [13.13, 114.87]
Tiffany 1993 (8)	27	12.4 (27.5396)	21	-1.6 (30.245)		27.9 %	14.00 [-2.59, 30.59]
Total (95% CI)	**750**		**710**			**100.0 %**	**17.40 [8.64, 26.17]**

Heterogeneity: Chi^2 = 14.08, df = 7 (P = 0.05); I^2 =50%

Test for overall effect: Z = 3.89 (P = 0.000099)

Test for subgroup differences: Not applicable



(1) Mean change at 180 mins

(2) Endpoint at 120 mins

(3) Endpoint at 'final timepoint'

(4) Endpoint at 60 mins

(5) Endpoint at 60 mins

(6) Endpoint at 240 mins

(7) Mean change at 45 mins. SD estimated from p value.

(8) Mean change at 20 mins. SD calculated from SEM

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Analysis 1.13. Comparison 1 IV MgSO4 versus placebo, Outcome 13 Borg Dyspnoea Scale score.

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 1 IV $MgSO_4$ versus placebo

Outcome: 13 Borg Dyspnoea Scale score

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bloch 1995 (1)	67	2.8 (1.9)	68	3 (2.2)			-0.20 [-0.89, 0.49]
Porter 2001 (2)	18	2.2 (4.65)	24	1.6 (4.65)			0.60 [-2.24, 3.44]
Silverman 2002 (3)	122	1.9 (2.1)	126	2 (2.1)			-0.10 [-0.62, 0.42]
Singh 2008 (4)	30	2 (0.83)	30	2.4 (1.35)			-0.40 [-0.97, 0.17]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**

Heterogeneity: $Chi^2 = 0.0$, df = 0 ($P<0.00001$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.0$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

(1) Borg Dyspnoea Scale at 120 mins

(2) Borg Dyspnoea Scale at 60 mins; SDs estimated from exact p-value

(3) Borg Dyspnoea Scale at 240 mins

(4) Borg Dyspnoea Scale at 120 mins

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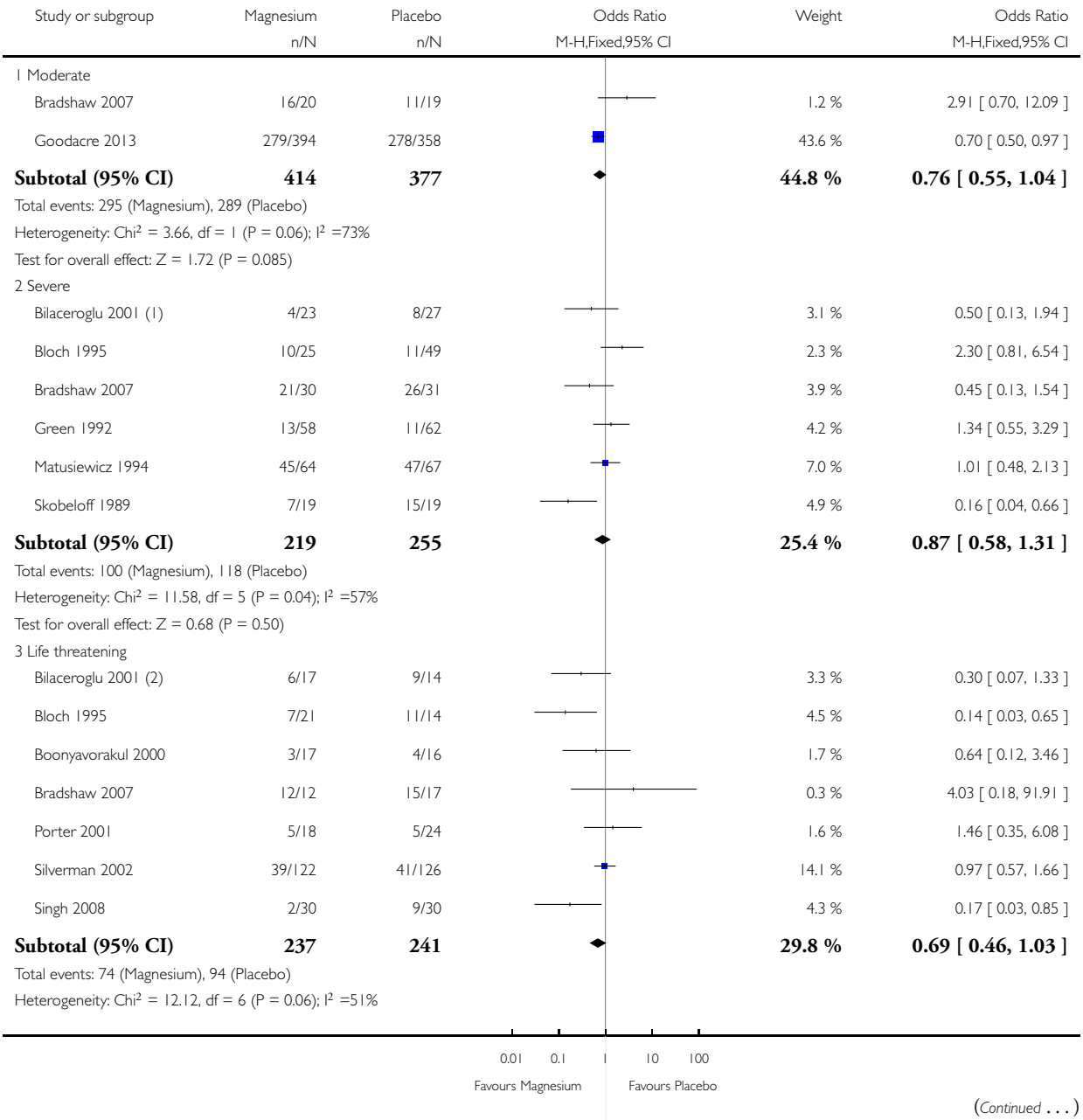
Analysis 2.1. Comparison 2 IV MgSO4 versus placebo (subgroup and sensitivity analyses), Outcome 1 Hospital admissions (by severity).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 2 IV $MgSO_4$ versus placebo (subgroup and sensitivity analyses)

Outcome: 1 Hospital admissions (by severity)



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Study or subgroup	Magnesium n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.82 (P = 0.068)					
Total (95% CI)	**870**	**873**	◆	**100.0 %**	**0.76 [0.62, 0.95]**
Total events: 469 (Magnesium), 501 (Placebo)					
Heterogeneity: Chi^2 = 27.95, df = 14 (P = 0.01); I^2 =50%					
Test for overall effect: Z = 2.48 (P = 0.013)					
Test for subgroup differences: Chi^2 = 0.63, df = 2 (P = 0.73), I^2 =0.0%					

(1) Moderate

(2) Severe

Analysis 2.2. Comparison 2 IV MgSO4 versus placebo (subgroup and sensitivity analyses), Outcome 2 Hospital admissions (by co-medications).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 2 IV $MgSO_4$ versus placebo (subgroup and sensitivity analyses)

Outcome: 2 Hospital admissions (by co-medications)

Study or subgroup	Magnesium n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Nebulised ipratropium bromide					
Bradshaw 2007 (1)	49/62	52/67		5.3 %	1.09 [0.47, 2.52]
Goodacre 2013	279/394	278/358		42.6 %	0.70 [0.50, 0.97]
Matusiewicz 1994	45/64	47/67		6.8 %	1.01 [0.48, 2.13]
Singh 2008	2/30	9/30		4.2 %	0.17 [0.03, 0.85]
Subtotal (95% CI)	**550**	**522**	◆	**58.9 %**	**0.73 [0.55, 0.96]**
Total events: 375 (Magnesium), 386 (Placebo)					
Heterogeneity: Chi^2 = 4.79, df = 3 (P = 0.19); I^2 =37%					
Test for overall effect: Z = 2.22 (P = 0.027)					
2 No nebulised ipratropium bromide					
Bilaceroglu 2001 (2)	10/40	17/41		6.3 %	0.47 [0.18, 1.21]
Bloch 1995 (3)	17/67	24/68		8.9 %	0.62 [0.30, 1.31]

(*Continued* . . .)

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(. . . *Continued*)

Study or subgroup	Magnesium n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Boonyavorakul 2000	3/17	4/16		1.7 %	0.64 [0.12, 3.46]
Green 1992	13/58	11/62		4.1 %	1.34 [0.55, 3.29]
Porter 2001	5/18	5/24		1.6 %	1.46 [0.35, 6.08]
Silverman 2002	39/122	41/126		13.8 %	0.97 [0.57, 1.66]
Skobeloff 1989	7/19	15/19		4.7 %	0.16 [0.04, 0.66]
Subtotal (95% CI)	**341**	**356**		**41.1 %**	**0.77 [0.55, 1.06]**
Total events: 94 (Magnesium), 117 (Placebo)					
Heterogeneity: Chi^2 = 9.09, df = 6 (P = 0.17); I^2 =34%					
Test for overall effect: Z = 1.58 (P = 0.11)					
Total (95% CI)	**891**	**878**		**100.0 %**	**0.75 [0.60, 0.92]**
Total events: 469 (Magnesium), 503 (Placebo)					
Heterogeneity: Chi^2 = 13.93, df = 10 (P = 0.18); I^2 =28%					
Test for overall effect: Z = 2.72 (P = 0.0066)					
Test for subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.82), I^2 =0.0%					

(1) All groups

(2) Moderate

(3) All groups

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Analysis 2.3. Comparison 2 IV MgSO4 versus placebo (subgroup and sensitivity analyses), Outcome 3 Hospital admissions (risk of bias sensitivity).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 2 IV $MgSO_4$ versus placebo (subgroup and sensitivity analyses)

Outcome: 3 Hospital admissions (risk of bias sensitivity)

Study or subgroup	Magnesium n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bloch 1995 (1)	17/67	24/68		10.8 %	0.62 [0.30, 1.31]
Boonyavorakul 2000	3/17	4/16		2.1 %	0.64 [0.12, 3.46]
Bradshaw 2007 (2)	49/62	52/67		6.3 %	1.09 [0.47, 2.52]
Goodacre 2013	279/394	278/358		51.5 %	0.70 [0.50, 0.97]
Porter 2001	5/18	5/24		1.9 %	1.46 [0.35, 6.08]
Silverman 2002	39/122	41/126		16.6 %	0.97 [0.57, 1.66]
Singh 2008	2/30	9/30		5.1 %	0.17 [0.03, 0.85]
Skobeloff 1989	7/19	15/19		5.7 %	0.16 [0.04, 0.66]
Total (95% CI)	**729**	**708**		**100.0 %**	**0.72 [0.57, 0.91]**

Total events: 401 (Magnesium), 428 (Placebo)

Heterogeneity: Chi^2 = 10.72, df = 7 (P = 0.15); I^2 =35%

Test for overall effect: Z = 2.79 (P = 0.0053)

Test for subgroup differences: Not applicable

(1) All groups

(2) All groups

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Analysis 2.4. Comparison 2 IV MgSO4 versus placebo (subgroup and sensitivity analyses), Outcome 4 Hospital admissions (unpublished sensitivity).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 2 IV $MgSO_4$ versus placebo (subgroup and sensitivity analyses)

Outcome: 4 Hospital admissions (unpublished sensitivity)

Study or subgroup	Magnesium n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bilaceroglu 2001 (1)	10/40	17/41		6.8 %	0.47 [0.18, 1.21]
Bloch 1995 (2)	17/67	24/68		9.6 %	0.62 [0.30, 1.31]
Boonyavorakul 2000	3/17	4/16		1.8 %	0.64 [0.12, 3.46]
Bradshaw 2007 (3)	49/62	52/67		5.6 %	1.09 [0.47, 2.52]
Goodacre 2013	279/394	278/358		45.7 %	0.70 [0.50, 0.97]
Green 1992	13/58	11/62		4.4 %	1.34 [0.55, 3.29]
Porter 2001	5/18	5/24		1.7 %	1.46 [0.35, 6.08]
Silverman 2002	39/122	41/126		14.8 %	0.97 [0.57, 1.66]
Singh 2008	2/30	9/30		4.5 %	0.17 [0.03, 0.85]
Skobeloff 1989	7/19	15/19		5.1 %	0.16 [0.04, 0.66]
Total (95% CI)	**827**	**811**		**100.0 %**	**0.73 [0.58, 0.91]**

Total events: 424 (Magnesium), 456 (Placebo)

Heterogeneity: Chi^2 = 13.30, df = 9 (P = 0.15); I^2 =32%

Test for overall effect: Z = 2.84 (P = 0.0046)

Test for subgroup differences: Not applicable

(1) Severe

(2) All groups

(3) All groups

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Analysis 2.5. Comparison 2 IV MgSO4 versus placebo (subgroup and sensitivity analyses), Outcome 5 PEF % predicted (Goodacre change score sensitivity).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 2 IV $MgSO_4$ versus placebo (subgroup and sensitivity analyses)

Outcome: 5 PEF % predicted (Goodacre change score sensitivity)

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bradshaw 2007 (1)	62	65.4 (21.0197)	67	62.8 (21.0197)		8.5 %	2.60 [-4.66, 9.86]
Goodacre 2013 (2)	394	14.4 (17.4)	358	14.4 (16.3)		77.4 %	0.0 [-2.41, 2.41]
Silverman 2002 (3)	122	62.7 (24.3)	126	53.1 (20.9)		14.1 %	9.60 [3.95, 15.25]
Total (95% CI)	**578**		**551**			**100.0 %**	**1.57 [-0.55, 3.69]**

Heterogeneity: Chi^2 = 9.47, df = 2 (P = 0.01); I^2 =79%

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable

(1) All groups at 60 mins

(2) at 120 mins

(3) at 240 mins

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Analysis 2.6. Comparison 2 IV MgSO4 versus placebo (subgroup and sensitivity analyses), Outcome 6 PEF L/min (Goodacre change score sensitivity).

Review: Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department

Comparison: 2 IV $MgSO_4$ versus placebo (subgroup and sensitivity analyses)

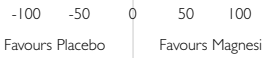
Outcome: 6 PEF L/min (Goodacre change score sensitivity)

Study or subgroup	Magnesium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bijani 2001 (1)	48	82.6 (40.1836)	33	47.8 (49.9777)		12.9 %	34.80 [14.31, 55.29]
Goodacre 2013 (2)	394	61 (73.6)	358	62.5 (69.4)		51.9 %	-1.50 [-11.72, 8.72]
Green 1992 (3)	58	263 (122)	62	278 (104)		3.3 %	-15.00 [-55.69, 25.69]
Matusiewicz 1994 (4)	64	279 (112)	67	256 (106.4096)		3.9 %	23.00 [-14.45, 60.45]
Porter 2001 (5)	18	211 (104)	24	252 (108)		1.3 %	-41.00 [-105.62, 23.62]
Silverman 2002 (6)	122	272 (144)	126	236 (123)		4.9 %	36.00 [2.62, 69.38]
Skobeloff 1989 (7)	19	72 (80)	19	8 (80)		2.1 %	64.00 [13.13, 114.87]
Tiffany 1993 (8)	27	12.4 (27.5396)	21	-1.6 (30.245)		19.7 %	14.00 [-2.59, 30.59]
Total (95% CI)	**750**		**710**			**100.0 %**	**9.44 [2.07, 16.81]**

Heterogeneity: Chi^2 = 21.65, df = 7 (P = 0.003); I^2 =68%

Test for overall effect: Z = 2.51 (P = 0.012)

Test for subgroup differences: Not applicable



(1) Mean change at 180 mins

(2) Endpoint at 120 mins

(3) Endpoint at 'final timepoint'

(4) Endpoint at 60 mins

(5) Endpoint at 60 mins

(6) Endpoint at 240 mins

(7) Mean change at 45 mins. SD estimated from p value.

(8) Mean change at 20 mins. SD calculated from SEM

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ADDITIONAL TABLES

Table 1. Summary of guideline treatment recommendations in acute asthma (adults)

	BTS/SIGN	GINA	NACA	NAEPP
Oxygen	√	√	√	√
Inhaled beta$_2$-agonist	√	√	√	√
Inhaled antimuscarinic	√	√	√	√
Sytemic corticosteroids	√	√	√	√
IV beta$_2$-agonist	(√) if nebulised form cannot be used reliably	x	√ if no response to inhaled form	x
IV $MgSO_4$	√	√	√ IV or nebulised	√
Heliox	x	x	x	√
IV aminophylline/ theophylline	(√) limited evidence, only after senior consultation	(√) if inhaled beta$_2$-agonist unavailable	(√) as an alternative to IV beta$_2$-agonist	x

BTS/SIGN: British Thoracic Society and Scottish Intercollegiate Guidelines Network joint guideline; GINA: Global Initiative for Asthma; IV: Intravenous; NACA: National Asthma Council Australia; NAEPP: National Asthma Education and Prevention Program; √: Recommended; x: Not recommended; (√): Recommended with conditions.

Table 2. Summary characteristics of included studies

Study ID	Country (centres)	Total N	Study design	Age range (years)	Dose (infusion)	Co-medications
Bijani 2001	Iran	81	R, DB, PC	12-85	25 mg/kg (30 minutes)	Nebulised SABA, IV xanthine, IV corticosteroid, O_2
Bilaceroglu 2001	Turkey	81	R, SB, PC	6-65	1 g or 2 g (unclear)	O_2 (if PaO_2 was < 60 mmHg)
Bloch 1995	USA (2)	149	R, DB, PC	18-65	2 g (20 minutes)	Nebulised SABA, IV corticosteroid
Boonyavorakul 2000	Thailand (1)	34	R, DB, PC	15-65	2 g (unclear)	Nebulised SABA, IV corticosteroid, O_2 if necessary

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Table 2. Summary characteristics of included studies (*Continued*)

Bradshaw 2007	Scotland (1)	129	R, DB, PC	16+	1.2 g (15 minutes)	Nebulised SABA, nebulised LAMA, IV corticosteroid, O_2
Del Castillo Rueda 1991	Spain (1)	16	R, DB, PC	?	1.5 g (15 minutes)	Nebulised SABA, IV corticosteroid
Goodacre 2013	UK (34)	1109	R, DB, PC	16+	2 g (20 minutes)	Nebulised SABA and LAMA, oral corticosteroid, O_2
Green 1992	USA (1)	137	?	18-65	2 g (20 minutes)	Nebulised SABA, IV corticosteroid (others at physician's discretion), O_2
Matusiewicz 1994	UK (1)	131	R	Adults	1.2 g (15 minutes)	Nebulised SABA and LAMA, O_2, IV corticosteroid (discretionary xanthine)
Porter 2001	USA (1)	42	R, DB, PC	18-55	2 g (unclear)	Nebulised SABA, IV corticosteroid, O_2
Silverman 2002	USA (8)	248	R, DB, PC	18-60	2 g (15 minutes)	Nebulised SABA, IV corticosteroid, O_2
Singh 2008	India (1)	70	R, SB, PC	18-60	2 g (20 minutes)	Nebulised SABA, nebulised LAMA, IV corticosteroid, O_2
Skobeloff 1989	USA (1)	38	R, DB, PC	18-70	1.2 g (20 minutes)	Nebulised SABA, IV metaproterenol, IV xanthine
Tiffany 1993	USA (1)	48	R, DB, PC	18-60	2 g (20 minutes)	Nebulised SABA, IV corticosteroid, SABA aerosol, IV xanthine

DB: Double-blind; IV: Intravenous; LAMA: Long-acting muscarinic antagonist; O_2: Oxygen; PaO_2: Partial pressure of oxygen in arterial blood; PC: Placebo-controlled; R: Randomised; SABA: Short-acting $beta_2$-agonist; SB: Single-blind.

Bilaceroglu 2001 included adults and children, but only 10 participants were younger than 18 years of age; mean age was 36 (± 13.4) years.

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Table 3. Baseline severity criteria

Study ID	Inclusion	Category within trial	PEF	FEV_1	Other	Classification*
Bijani 2001	PEF < 200 after bronchodilator and corticosteroids	All participants	31% predicted	-	RR = 35 rpm	Life threatening
Bilaceroglu 2001	PEF increasing < 50% or FEV_1 < 75% predicted after single salbutamol	Moderate	57% predicted	43% predicted	PaO_2 = 69 mmHg	Severe
		Severe	32% predicted	32% predicted	PaO_2 = 64 mmHg	Life threatening
Bloch 1995	FEV_1 < 75% predicted after single salbutamol	Moderate	-	40% predicted	-	Severe
		Severe	-	20% predicted	-	Life threatening
Boonyavorakul 2000	Composite severity score	All participants	-	-	RR = 33 rpm HR = 125 bpm	Life threatening
Bradshaw 2007	PEF < 75% predicted	Moderate	60% predicted 248 L/min	-	HR = 102 bpm	Moderate
		Severe	41% predicted 170 L/min	-	HR = 109 bpm	Severe
		Life threatening	23% predicted 96 L/min	-	HR = 116 bpm	Life threatening
Del Castillo Rueda 1991	-	All participants	-	-	-	Unknown (not in analysis)
Goodacre 2013	One or more of the following: PEF < 50% predicted; RR > 25, HR > 110 or cannot complete sentences, but not life threatening	All participants	52% predicted 433 L/min	-	-	Moderate
Green 1992	-	All participants	143 L/min	-	RR = 29 rpm HR = 108 bpm	Severe

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Table 3. Baseline severity criteria (*Continued*)

Matusiewicz 1994	PEF < 250 L/min or < 50% predicted	All participants	-	-	-	Severe
Porter 2001	PEF < 100 L/min or < 25% predicted	All participants	88.5 L/min	-	RR = 31 rpm HR = 110 bpm	Life threatening
Silverman 2002	FEV_1 < 30% predicted	All participants	27% predicted 143 L/min	23% predicted	HR = 102 bpm	Life threatening
Singh 2008	FEV_1 < 30% predicted	All participants	22% predicted	38% predicted	HR = 127 bpm	Life threatening
Skobeloff 1989	PEF < 200 L/min, not doubled after beta-agonist, IV corticosteroid, theophylline	All participants	~150 L/min (from graph)	-	HR = ~ 100 bpm from graph RR = ~ 28	Severe
Tiffany 1993	PEF < 200 L/min, not doubled after albuterol × 2	All participants	115 L/min	0.95 L	-	Life threatening

bpm: Beats per minute; FEV_1: Forced expiratory volume in 1 second; HR: Heart rate; PaO_2: Partial pressure of oxygen in arterial blood; PEF: Peak expiratory flow; rpm: Respirations per minute;RR: Respiration rate..

Classification for the severity subgroup analysis was assigned by an independent clinician and was cross-checked with study authors' own judgements. Discrepancies were resolved through discussion.

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APPENDICES

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

Electronic searches: core databases

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

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
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

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MEDLINE search strategy used to identify trials for the CAGR

Asthma search

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

Filter to identify RCTs

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

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

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

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 magnesium*
#6 MgSO4
#7 #5 or #6
#8 #4 and #7
#9 (#8) AND (INREGISTER)

[Note: in search line #1, MISC1 refers to the field in which the reference record has been coded for condition, in this case, asthma]

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CONTRIBUTIONS OF AUTHORS

All review authors contributed to all aspects of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

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External sources

- KK, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We could not carry out the prespecified subgroup analysis based on age, as no studies had a mean participant age above 65 years. For the severity subgroup analysis, we renamed the categories from mild, moderate and severe to moderate, severe and life threatening to fit with BTS/SIGN 2012 classifications. For the co-medications subgroup analysis, we changed the labelling from 'maximal and minimal' to 'with and without ipratropium bromide' so as not to imply preference of one strategy over the other (definitions remained the same). We considered a meta-analysis of O_2 saturations to be not viable. We added a post-hoc sensitivity analysis using change from baseline instead of endpoint means from Goodacre 2013, as baseline imbalances were noted in this study.

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