Inhaled sodium cromoglycate for asthma in children (Review)

van der Wouden JC, Uijen JHJM, Bernsen RMD, Tasche MJA, de Jongste JC, Ducharme FM


www.cochranelibrary.com
# Table of Contents

1. Header ................................................................. 1
2. Abstract ............................................................. 1
3. Plain Language Summary ........................................... 2
4. Background .......................................................... 2
5. Objectives ........................................................... 2
6. Methods .............................................................. 2
7. Results ............................................................... 4
   - Figure 1 .......................................................... 6
   - Figure 2 .......................................................... 7
   - Figure 3 .......................................................... 8
   - Figure 4 .......................................................... 9
   - Figure 5 .......................................................... 10
   - Figure 6 .......................................................... 11
   - Figure 7 .......................................................... 13
8. Discussion ........................................................... 13
9. Authors' Conclusions ............................................... 15
10. Acknowledgements ................................................ 15
11. References ........................................................ 16
12. Characteristics of Studies ......................................... 25
13. Data and Analyses .................................................. 52
14. Additional Tables .................................................. 52
15. Feedback ............................................................ 62
16. What's New ........................................................ 63
17. History .............................................................. 64
18. Contributions of Authors .......................................... 65
19. Declarations of Interest .......................................... 65
20. Sources of Support ................................................ 65
21. Index Terms ........................................................ 65
**Abstract**

Sodium cromoglycate has been recommended as maintenance treatment for childhood asthma for many years. Its use has decreased since 1990, when inhaled corticosteroids became popular, but it is still used in many countries.

**Objectives**

To determine the efficacy of sodium cromoglycate compared to placebo in the prophylactic treatment of children with asthma.

**Search methods**

We searched the Cochrane Airways Group Trials Register (October 2009), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2009), MEDLINE (January 1966 to October 2009), EMBASE (January 1985 to October 2009) and reference lists of articles. We also contacted the pharmaceutical company manufacturing sodium cromoglycate.

**Selection criteria**

All double-blind, placebo-controlled randomised trials, which addressed the effectiveness of inhaled sodium cromoglycate as maintenance therapy, studying children aged 0 up to 18 years with asthma.

**Data collection and analysis**

Two authors independently assessed trial quality and extracted data. We pooled study results.

**Main results**

Of 3500 titles retrieved from the literature, 24 papers reporting on 23 studies could be included in the review. The studies were published between 1970 and 1997 and together included 1026 participants. Most were cross-over studies. Few studies provided sufficient information to judge the concealment of allocation. Four studies provided results for the percentage of symptom-free days. Pooling the results did not reveal a statistically significant difference between sodium cromoglycate and placebo. For the other pooled outcomes, most of the symptom-related outcomes and bronchodilator use showed statistically significant results, but treatment effects were small. Considering the confidence intervals of the outcome measures, a clinically relevant effect of sodium cromoglycate cannot be excluded. The funnel plot showed an under-representation of small studies with negative results, suggesting publication bias.
Authors’ conclusions

There is insufficient evidence to be sure about the efficacy of sodium cromoglycate over placebo. Publication bias is likely to have overestimated the beneficial effects of sodium cromoglycate as maintenance therapy in childhood asthma.

Plain Language Summary

The effects of sodium cromoglycate compared with placebo for chronic asthma in children

In this review we aimed to determine whether there is evidence for the effectiveness of inhaled sodium cromoglycate as maintenance treatment in children with chronic asthma. Most of the studies were carried out in small groups of patients. Furthermore, we suspect that not all studies undertaken have been published. The results show that there is insufficient evidence to be sure about the beneficial effect of sodium cromoglycate compared to placebo. However, for several outcome measures the results favoured sodium cromoglycate.

Background

Since the late 1960s, disodium cromoglycate (DSCG) has been used as maintenance treatment for children with moderate asthma, although the precise mechanism of action is still not fully understood. No serious side effects have been reported in trials, but cases of dysuria, urticaria, bronchospasm, angio-oedema and anaphylaxis have been ascribed to the use of DSCG, once with death as a result (Lester 1997; Leynadier 1985).

In the early 1990s, many guidelines recommended use of DSCG. Gradually, corticosteroids have come to the fore as first choice maintenance therapy (BAG 1997; Ernst 1996), or were recommended alongside DSCG for mild persistent asthma (NIH 1997). Other guidelines continued to recommend DSCG as first choice in young children (Sly 1997). The most recent revisions of the GINA and NIH guidelines (GINA 2005; NIH 2002) consider the role of DSCG in children to be limited. Inhaled glucocorticosteroids are the first choice; DSCG is only recommended as one of the alternative treatment options for children with mild persistent asthma. Canadian guidelines no longer recommend DSCG as maintenance therapy for children, nor do British guidelines for children aged 5 to 12 years (Becker 2005; BTS 2003, page i20).

The long-term side effects of asthma treatment with inhaled steroids in early childhood are not clear. Nevertheless, there is concern that treating very mild cases of asthma with inhaled steroids may have an adverse effect on the balance between risk and benefit. A Cochrane review has shown an effect of inhaled beclomethasone on linear growth in children (Sharek 1999). Therefore, physicians involved in the treatment of asthma in children may still prefer sodium cromoglycate as first choice maintenance treatment.

The use of DSCG has decreased since 1990, while the use of inhaled corticosteroids is increasing. The discrepancy between guidelines and the debate on the role of DSCG, which led to its recent withdrawal as first line maintenance treatment in young children in some countries, was the rationale to review the efficacy of inhaled DSCG as maintenance treatment for chronic childhood asthma.

Objectives

To determine whether there is evidence for the efficacy of inhaled sodium cromoglycate as maintenance treatment in children with asthma.

Methods

Criteria for considering studies for this review

Types of studies
All double-blind, placebo-controlled, randomised clinical trials, which addressed the effectiveness of DSCG as maintenance therapy.

Types of participants
Children aged 0 up to 18 years with asthma in all settings (general practice, emergency departments, outpatient departments, hospitalised). We only included studies including both children and adults when results for children were presented separately. When
the number of children in these studies was less than five, we did not include the study.

**Types of interventions**

Inhaled sodium cromoglycate, delivered via any device: nebulised, by Spinhaler or by metered dose inhaler, with or without holding chamber. We only included trials that compared DSCG with placebo. No co-interventions were permitted other than rescue medication as needed.

**Types of outcome measures**

**Primary outcomes**

The primary outcome measure was the difference in percentage of days without asthma symptoms, between placebo and cromoglycate treatment.

**Secondary outcomes**

- Symptom scores (day cough, day wheeze, daytime asthma score, day activity, night cough, night wheeze, night-time asthma score, sleep disturbance, overall symptom/severity score)
- Auscultation score
- Preference of patients/parents and clinicians
- Overall success rate
- Bronchodilator use, use of oral steroids, hospital admission
- Side effects

**Search methods for identification of studies**

**Electronic searches**

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group Module for further details).

Additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3, 2009), MEDLINE (January 1966 to October 2009) and EMBASE (1979 to October 2009) were also conducted. For MEDLINE and EMBASE we used the Cochrane sensitive search strategy to select all RCTs (Dickersin 1994) and in all databases, we used the following search terms: cromolyn* OR dscg OR cromoglycate* or cromoglicate* OR cromone* or intal*

Searches are current to October 2009.

**Searching other resources**

We contacted the pharmaceutical company manufacturing DSCG (Rhone-Poulenc-Rorer, formerly Fisons plc, Loughborough, UK), checked bibliographies of retrieved trials and contacted primary authors of trials published after 1990 for any additional trials.

**Data collection and analysis**

**Data extraction and management**

Two authors extracted data. When using symptom scores, most studies used a scale of 0 to 3 points; where a different scale was used we transformed the mean and standard deviation for our purposes. We calculated confidence intervals for the treatment effect (difference in symptom score) for individual studies assuming a t-distribution.

**Assessment of risk of bias in included studies**

Two authors independently scored the methodological quality of all trials using three sets of criteria: Chalmers (Chalmers 1981), Jadad (Jadad 1996) and the Cochrane criteria for concealment. A third author determined the final decision if there was lack of consensus. Trials in which one of the authors was involved were also scored by an impartial author. We did not contact authors of the trials for confirmation of methodology and data extraction, because most of the studies were performed many years ago and we considered it unlikely that this would provide further useful information. When updating the review in 2007, a 'Risk of Bias' table was added (Figure 1).

**Dealing with missing data**

If no standard error of the treatment effect of a particular outcome measure was available, and could not be calculated, we imputed it from a study with a similar design (cross-over or parallel) (cf Follman 1999). If more than one study was available for imputation, we selected the largest study, unless this choice would lead to inconsistencies with the results in the original study (e.g. when the authors reported no significant difference, but the imputed data would change this). In that case the second largest study was taken.

**Data synthesis**

We computed pooled estimates of the treatment effect and the pooled 95% confidence intervals (CI), combining parallel and cross-over studies (Elbourne 2002). For cross-over studies we used
the results of paired analyses, extracting treatment effect, standard error and within patient correlation between DSCG and placebo period (rho) from papers. When rho was not given, we imputed this in the same way as stated above for missing standard errors. We tested for homogeneity (Dersimonian 1986). When heterogeneity was found (P < 0.05), we did not use the fixed-effect model to compute a pooled estimate and confidence interval, but only used the random-effects model (Dersimonian 1986). To investigate causes for heterogeneity, we evaluated the influence of study characteristics (year of publication, mean age of children, method of delivery, asthma severity of the study population, methodological quality, doses per day and duration). Assessment of asthma severity was based on the description of the study population in the papers (see ‘Characteristics of included studies’ table). As there was no single outcome measure available for all studies, we selected those outcomes for which at least 10 studies were available. To include as many studies as possible in the funnel plot (see below) and the meta-regression analysis, we combined various outcome measures that used a similar scale, taking the first available from overall symptom score, day wheeze, day cough, day activity and daytime asthma score. 

For all study characteristics except asthma severity, we used univariate and multivariate meta-regression analysis (Fleiss 1993), weighing observations by the reciprocal of the square of the standard error of the mean difference between placebo and DSCG. Thus, all pooled outcomes are presented as weighted mean differences (WMD). Study characteristics were either entered as categorical (design, type of delivery) or as continuous (publication year, quality score, etc.). For asthma severity, as we used the asthma score in the placebo group (or period) as study characteristic. Because this measure is subject to measurement error as much as the outcome variables are, ordinary regression analysis is inappropriate, as this technique only assumes measurement error in the outcome variable. Therefore, we used an analysis technique called functional relationships (Nagelkerke 1992) to evaluate the influence of asthma severity of the study population on the outcome for cough, wheeze and overall symptom score.

We performed all analyses using SPSS version 10 for the initial review.

**Subgroup analysis and investigation of heterogeneity**

We performed subgroup analyses when outcome data were available from at least 10 studies, using the following characteristics for subgroup identification: asthma severity (moderate versus severe), health care settings (hospitalised/institutionalised versus other settings), type of delivery (nebulised versus other), age (using a mean age of five years as the cut-off point), duration of follow up (using three months follow up as the cut-off point) and methodological quality (for Jadad’s scoring system three points or higher versus lower; for Chalmers’ summed items the 13 best studies versus the remaining studies).

To explore heterogeneity further and visualise possible publication bias, we constructed a funnel plot of the effect estimate (delta) against the precision (Egger 1995), using the same combination of outcome measures as for meta-regression analysis. The precision of a trial was defined as one divided by the standard error. The symmetry of the funnel plot was tested using a significance level of 0.10 (Egger 1997).

**RESULTS**

**Description of studies**

**Results of the search**

Searching the literature databases resulted in retrieval of over 3500 titles (MEDLINE: 1500; EMBASE: 1400; Cochrane Airways Group Trials Register: 850 titles). We read about 200 papers in full; 65 of these were evaluated by two authors according to a structured inclusion criteria form. The final set consisted of 24 papers, reporting on 23 studies. For one study, two papers were published reporting on different outcome measures (Yuksel 1992). Update searches were conducted in November 2006 and October 2007. These identified 181 titles, which were screened, and 10 were obtained as full papers for further assessment. None of these fulfilled our inclusion criteria, but several were added to the list of excluded studies. An updated search in October 2008 did not identify any new studies for consideration in the review. The latest search was in July 2010 and it did not return any eligible studies although two studies were added to Characteristics of excluded studies.

**Included studies**

Most of the included studies were European (13 studies, nine of which were from the UK) or North American. Two were from Israel, three from Japan and one from Thailand. All but three papers were written in English. One study was in Norwegian (Dalene 1977), the other two in Japanese (Kobayashi 1970; Mikawa 1986).

The studies were published between 1970 and 1997. Twelve studies were published in the 1970s, eight studies in the 1980s, and four in the 1990s. Detailed information on each study is given in the table of ‘Characteristics of included studies’.

The age range of the children in the included studies varied considerably. Eleven studies included children not older than four years of age. In one study (Easton 1973) the age of the children was not specified. Before 1977, none of the studies included children below the age of four.

Most of the studies had a cross-over design. Four were parallel group studies. The cross-over studies typically were divided into...
two periods of three or four weeks treatment, with sometimes a washout period in between. In some of the cross-over studies, the first two weeks of each period were ignored in the analysis.

In nine studies the study drugs (DSCG or placebo) were nebulised. Nine studies used dry powder in capsules, most often with the Spinhaler as device, but sometimes without a device being mentioned. In five studies the drugs were administered as aerosols with a spacer and sometimes a facemask.

In several papers it was not clear whether and what concurrent medication was permitted during the trial. We included these studies. Compliance with the therapy regimen was only discussed in a minority of papers.

Most of the studies were carried out in a hospital setting, usually with outpatients. For several studies, no information about the setting could be found. Based on the authors’ affiliations, we assumed that these were hospital outpatients. In these cases we have added a question mark after 'hospital outpatients' in the table of study characteristics. Only one study recruited patients in general practice (Tasche 1997).

Regarding asthma severity, most of the studies included children that would be classified as having moderate or severe asthma by current standards (e.g. GINA 2005). Many children had one or more hospital admissions for asthma in the past. The three studies with probably the largest proportion of mild asthmatic children were Edmunds 1980; Furfaro 1994 and Tasche 1997.

The size of the trials varied between 10 and 232 participants. Only two trials included more than 100 children (Mikawa 1986; Tasche 1997). As can be expected, the parallel-group trials had larger patient groups than the cross-over trials (parallel group trials had on average 131 participants versus 26 for cross-over studies). Altogether, the 23 studies included 1026 participants.

The length of the period during which the children used either active medication or placebo in the trials varied from three weeks to 26 weeks. For 15 studies (of which 14 had a cross-over design), this was three or four weeks, while only two studies had a duration of over 10 weeks (Cogswell 1985; Tasche 1997).

Several study characteristics were strongly correlated. Dose (corrected for type of delivery), method of delivery, year of publication, age of children and length of treatment period showed Pearson correlations up to 0.75.

The variety of outcome measures on which data were reported was large. Likewise, for most outcome measures only few studies reported comparable data. The outcome measures that were reported most often were asthma scores (10 studies), daytime wheeze scores (10 studies), daytime cough scores (nine studies) and bronchodilator use (10 studies). Several studies reporting on hospital admittance and steroid use provided insufficient information to be included in the pooled results.

**Excluded studies**

Excluded studies were either not blinded, not randomised, not placebo-controlled, did not concern the appropriate age group, or investigated the effectiveness of DSCG in exercise induced asthma. One study (Kraemer 1993) was misclassified and hence erroneously included in the first version of the review: this trial was removed from this update (see 'Characteristics of excluded studies').

**Risk of bias in included studies**

See: table ‘Characteristics of included studies’.

The methodological quality, as assessed by two scoring methods, varied considerably (see Table 1; Table 2). Only one study attained the maximum score of five points on the Jadad list (Mikawa 1986). The proportion of items fulfilled on Chalmers’ s list varied between 24 and 79% (mean 44% (SD 11.9)). Of the papers reporting cross-over studies, only few stated explicitly that the sequence of both treatments had been randomised. In the analysis, we assumed they were.

When updating the review in 2007, ‘Risk of Bias’ tables were produced, and a summary table was added to this review (Figure 1). For further explanation of this table, see the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8 (Higgins 2008).
**Figure 1. Methodological quality summary: review authors’ judgments about each methodological quality item for each included study.**

|------------------|-------------------------------|-------------------------|-----------|-----------------------------------|-----------------------------|--------------------|
For several items (sequence generation, allocation concealment, selective reporting and other sources of bias), only few studies provided a clear answer. The proportion of question marks (for which the study reports do not provide enough information) is high. Blinding was considered to be adequate for all studies, which is no surprise, as this was an inclusion criterion. Several studies inadequately reported on incomplete outcome data or reported selectively. None of the studies attained the maximum score for ‘withdrawals’, and 20 of the 23 studies scored less than 50% on this item (Table 1).

Effects of interventions

Study outcomes have been gathered into Additional tables 3 to 19 and summarised in Table 20. The tables give pooled point estimates for the difference between DSCG and placebo (i.e. DSCG minus placebo), and confidence intervals, assuming homogeneity (fixed-effect) and heterogeneity (random-effects). Below we report the results for the outcome measures for which a considerable number of studies were available. These study outcomes are now also shown as forest plots for the primary outcome measure and all secondary outcomes with more than five contributing studies.

Symptoms

Only four studies provided results for the percentage of symptom-free days: our primary outcome measure (Figure 2; Table 3). In all but one of the studies (Cogswell 1985), the confidence interval included the point of no difference. Pooling the results revealed no significant difference between DSCG and placebo (WMD 6.76% favouring DSCG, 95% CI -2.18 to 15.70), random-effects model.

**Figure 2. Forest plot of the primary outcome of the review: mean difference in % symptom-free days between sodium cromoglycate and placebo**

<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage of symptom-free days (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cogswell 1985</td>
<td>&lt;</td>
</tr>
<tr>
<td>Edmunds 1980</td>
<td>&lt;</td>
</tr>
<tr>
<td>Henry 1984</td>
<td>&lt;</td>
</tr>
<tr>
<td>Tasche 1997</td>
<td>&lt;</td>
</tr>
<tr>
<td>Total FEM</td>
<td>&lt;</td>
</tr>
<tr>
<td>Total REM</td>
<td>&lt;</td>
</tr>
<tr>
<td>favour placebo</td>
<td>&lt;</td>
</tr>
<tr>
<td>favour DSCG</td>
<td>&lt;</td>
</tr>
</tbody>
</table>

A variety of other symptom and hindrance scores was found. In tables 4 to 19 we present the results for outcome measures for which at least two studies provided data. Here we describe the results for the symptom scores with the largest number of studies: day cough score (nine studies), day wheeze score (10 studies), and overall symptom/severity score (10 studies).

For daytime cough, the difference between placebo and DSCG favoured DSCG in all but one study (Bertelsen 1986) (Figure 3; Table 4). The confidence intervals included the point of no difference for seven out of the nine studies. Pooling the results (random-effects model because of heterogeneity) did result in a sta...
tically significant difference between placebo and DSCG favour-
ing DSCG (WMD -0.18, 95% CI -0.32 to -0.04).

**Figure 3. Forest plot of mean difference in symptom scores for day cough between sodium cromoglycate and placebo**

![Forest plot](image)

For daytime wheeze the pooled results show a small but significant difference favouring DSCG: a difference of -0.11 (WMD) on a scale of 0 to 3 (95% CI -0.19 to -0.03; random-effects model) (Figure 4; Table 5).

---

Inhaled sodium cromoglycate for asthma in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Figure 4. Forest plot of mean difference in symptom scores for day wheeze between sodium cromoglycate and placebo

day wheeze score (95% CI)

favours DSCG <  > favours placebo
Mean overall symptom scores favoured DSCG in direction in six out of ten studies (Figure 5; Table 6). The 95% confidence intervals of four of the studies included the point of no difference. Pooling the results (test of homogeneity rejected, hence random-effects model) showed an overall mean difference of -0.22 symptom score points (WMD), favouring the DSCG group (95% CI -0.34 to -0.09), hence statistically significant.

Figure 5. Forest plot of mean difference in overall symptoms between sodium cromoglycate and placebo
Use of other medication

The use of bronchodilators was reported in ten studies (Figure 6; Table 7). Seven of these reported a difference in favour of DSCG. Five of the studies had confidence intervals excluding the point of no difference. Pooling the data (null hypothesis of homogeneity rejected) resulted in an overall estimated difference of -0.24 daily doses (WMD) favouring the DSCG group (95% CI -0.07 to -0.42, random-effects model), which is statistically significant.

Figure 6. Forest plot of mean difference in bronchodilator use between sodium cromoglycate and placebo

Bronchodilator use (doses per day) (95% CI)

favourites DSCG < > favours placebo
Steroid use in case of exacerbations was also addressed as an outcome measure: systemic or inhaled, or sometimes unspecified. Seven studies provided these data (Table 8). Only one study (Shioda 1970) found a significant difference. The pooled results did not show a significant difference (OR 0.76, 95% CI 0.34 to 1.72).

**Hospital admission**

Hospital admission was reported in three studies (Table 9). None of these found a significant difference between DSCG and placebo. Pooling the results of the parallel studies did not result in a significant difference (OR 0.93, 95% CI 0.40 to 2.56).

**Lung function parameters**

Thirteen studies assessed lung function parameters. Eight of these reported no statistically significant difference between DSCG and placebo groups/periods, sometimes without providing exact figures. The variety of parameters, methods used, time of day tests were performed and the way they were presented made it impossible to pool data. Five of the 13 studies reported differences to be statistically significant for one or more lung function parameters (Geller 1983; Hiller 1975; Limburg 1971; Matthew 1977; Yüksel 1992).

**Side effects**

Twelve studies did not report on side effects (Table 10). The reported side effects of DSCG and placebo in the other 11 studies were mild and of short duration (minutes to a few days). Overall, differences between DCSG and placebo were small.

**Subgroup analysis**

Subgroup analyses were performed for four outcome measures: day time wheeze (10 studies), overall asthma symptom/severity score (10 studies), bronchodilator use (10 studies) and a combination of outcome measures using the same scale (19 studies, see ‘Data collection and analysis’). For day time wheeze and for bronchodilator use, the differences between subgroups were either not significant or one of the groups contained only one or two studies. For the asthma symptom/severity score, the age of the children and duration of follow up showed statistically significant differences. Studies that included children with a mean age lower than five showed less effect than studies that (also) included older children (estimate of difference between DSCG and placebo -0.06 (95% CI -0.15 to 0.02) versus -0.30 (95% CI -0.49 to -0.11), favouring DSCG, P = 0.03). The three studies that had at least three months follow up showed less effect than the eight shorter studies (0.04 versus 0.27, favouring DSCG, P = 0.01).

The combined outcome measure showed subgroup differences for way of administration of the drug, hospitalisation, age and duration of follow up. Studies that applied nebulised DSCG showed less effect than studies that used other methods of administration (0.08 versus 0.32 on a 0 to 3 point symptom scale, P = 0.01). Studies in hospitalised patients showed less effect than studies in other patients (0.08 versus 0.34, P = 0.01). Subgroup analyses for age and for duration of follow up both showed differences of the same magnitude and in the same direction for the combined outcome measure as reported above for asthma symptom/severity score.

The subgroup analyses for the above mentioned four outcome measures were also performed separately for studies with higher methodological quality (see ‘Data collection and analysis’ for cutoffs). Comparing the results of this subgroup of studies to the overall results revealed only minor differences, in the same direction as in our primary analysis, sometimes more in favour of the subgroup of better quality studies.

The same analyses were done excluding cross-over studies that did not take account of period effects (or did not report they did). For the asthma symptom score (five studies) the pooled difference was -0.06, with 95% CI (-0.16 to 0.03) (random-effects model). For bronchodilator use (four studies) the pooled difference was -0.05 doses (-0.12 to 0.02) (fixed-effect), the random-effects model gave -0.08 (-0.19 to 0.04), all not statistically significant. Both these outcomes are smaller than found for the whole group of studies (see Tables). For the combined outcome measures (see ‘Data collection and analysis’) nine studies provided data. The mean difference was -0.20, with random-effects, 95% CI -0.49 to 0.09.

**Funnel plot**

For the funnel plot, showing the mean difference in effect between DSCG and placebo treatment against precision of the study, we could include 19 studies. The symmetry test gave a value of -1.95 for the constant (SE 1.12, P = 0.09), which means that the hypothesis of symmetry was rejected. Especially imprecise (small or heterogeneous) studies with results favouring placebo were underrepresented (Figure 7).
**Meta-regression analysis and functional relationships**

Seven study characteristics showed relationships with the (combined) outcome variable ($P < 0.25$). As only 19 studies provided data for this combined outcome measure, the power of a meta-regression analysis would be very low. Furthermore, several study characteristics were strongly related to each other (e.g. age, publication year, and method of administration of DSCG). Hence, we decided to refrain from the planned analysis.

There was no influence of placebo symptom level on study outcomes (day cough, day wheeze, overall severity score and bronchodilator use), assessed by means of functional relationships.

**DISCUSSION**

**Summary of main results**

This systematic review, involving 1026 children in 23 trials performed between 1970 and 1997, provides conflicting evidence regarding the superiority of DSCG over placebo in children with asthma. There is no evidence to support the superiority of DSCG over placebo in the percentage of symptom-free days, the main outcome of this review, although this is limited by the small number of trials reporting on this outcome.

For several secondary outcomes, especially symptom scores and bronchodilator use, we found significant group differences between DSCG and placebo, favouring DSCG. The overall treatment effect for these outcomes appears to be quite small, with a mean difference of 0.2 to 0.3 symptom score on a scale from 0 to 3 and less than ¼ puff per day for bronchodilator use. However, considering the confidence intervals of the outcome measures, a
clinically relevant effect of sodium cromoglycate cannot be es-
cluded.
For mild persistent asthma, evidence is only available for children 
below the age of four. For this subgroup, we can rule out important 
benefit in terms of symptom scales but not in terms of symptom-
free days. We cannot rule out the possibility that DSCG is of 
benefit in children above the age of four.

Overall completeness and applicability of 
evidence
Although DSCG has been advocated as maintenance treatment for 
mild to moderate asthma, and nowadays only for mild persistent 
asthma (GINA 2005), nearly all trials were hospital based, and 
included children with moderate to severe asthma. Three studies 
appear to have included a considerable proportion of children with 
mild asthma (Edmunds 1980; Furfaro 1994; Tasche 1997). The 
study by Edmunds showed positive outcomes on four outcome 
measures but was methodologically weak. The two other studies 
had negative conclusions, i.e. DSCG was not more effective than 
placebo. Both studies were carried out in young children (below 
the age of four). Studies in children above the age of five found 
more favourable effects than studies in children below that age.
In nine studies, the drug was administered with a nebuliser. Spin-
halers were used in eight studies. Metered dose inhalers with spacer 
devices, nowadays the preferred method of administration for 
young children, were used in only two studies (Tasche 1997; Y uksel 1992). The method of administration, a critical factor in delivery 
of drugs to the lungs, was a predictor of outcome (combined out-
come measure): studies that used nebulisation showed less effect 
than studies that used other methods.
The year of publication of the study and the age of the children 
turned out to be strongly related. In multivariate analysis, results 
proved to be instable, sometimes favouring age, sometimes pub-
lication year. It is impossible to disentangle these two factors: in 
the early days of DSCG, studies were carried out in older children 
and only after 1977 did studies start to include children below the 
age of four.

Quality of the evidence
Heterogeneity of study results is apparent for several outcome 
measures. The methodological quality of the studies, especially 
regarding sequence generation and concealment of allocation, was 
often impossible to assess (see 'Risk of Bias' table Figure 1), and 
varied considerably for other aspects. 
The absence of small trials favouring placebo, as shown in the 
funnel plot, indicates possible publication bias. This bias is likely 
to result in an overestimation of the efficacy of DSCG, especially 
because when applying a random-effects model the small positive 
studies we included received a relatively large weight.

Potential biases in the review process
It has been questioned whether the (difference in) percentage of 
symptom-free days should be the primary outcome measure, given 
the fact that only a minority of studies included this (see Feedback 
(Edwards et al)). However, we believe that the choice of primary 
outcome measure should not be driven by availability, but by clin-
ical relevance. We feel supported by national and international 
guidelines, where the aim of the treatment of asthma focuses on 
leading a normal life with few or no complaints. 
Lung function parameters could not be aggregated due to incom-
plete reporting of data.

Agreements and disagreements with other 
studies or reviews
The effects of treatment with DSCG have been reviewed previ-
ously. As early as 1974 a narrative review was published in JAMA 
(Dykes 1974), based on data provided by the manufacturers, but 
giving no references to published data. Edwards 1994 examined 
the evidence for the anti-inflammatory action of DSCG in adults 
and children in a large number of controlled and uncontrolled 
but it is unclear how these were selected. Hoag 1991 sum-
marised studies on the effect of DSCG on bronchial hyperre-
activity in adults and children. Schweitzer 1994 discussed the 
role of DSCG in children below two years of age and concluded 
that evidence was lacking: this conclusion was shared by Carlsen 1996. Holgate 1996 reviewed recent trials with metered dose in-
halers in children and adults and discussed challenge studies, ther-
apeutic studies, and the long-term effects of DSCG. Other re-
views were Berman 1983; Carlsen 1996; Church 1985; Kuzemko 1989; Shapiro 1985; Storms 2005. None of the reviews men-
tioned above were systematic, assessed the methodological quality 
of studies or tried to quantify treatment effects. With the excep-
tion of Schweitzer 1994, all of these reviews came to conclusions 
in favour of DSCG.
Our group published a systematic review of inhaled DSCG as 
maintenance therapy in children in 2000 (Tasche 2000). The cur-
rent review differs from the previous one in several respects. Seven 
studies that were included in the previous review were excluded 
in this one, either because of different exclusion criteria, espe-
sionary use of steroids (Crisp 1974; Fox 1972; Hyde 1973; Miraglia 1982; Sly 1970), or because we initially 
looked the fact that the placebo drug contained isoprenaline 
and hence was not a true placebo (Silverman 1972; Smith 1968).
The current review included six studies that were not included 
in the previous one, because of more thorough searching and the 
withdrawal of language restrictions (Easton 1973; Dalene 1977; 
Another important difference is that the previous review only con-
sidered symptom scores for cough and wheeze as outcome 
measures. The overall results of the previous and the first version of
the current review are similar. For the 2007 update, changing our focus for the pooled results from the tolerance interval to the random-effects model interval has slightly affected the interpretation of our results in favour of DSCG. For this update, we excluded Kraemer 1993, for reasons mentioned above.

The funnel plot was similar to the one published in our earlier review (for ‘wheeze’), although a different outcome was used in order to include as many studies as possible (Figure 7). As we have put forward before, when discussing our previous review (Tasche 2000; Tasche 2001), publication bias may be an explanation for the asymmetry. More specifically we think it is possible that small studies that did not find a beneficial effect for DSCG may not have been submitted to journals, or may not have been published. In order to appreciate the results of this review in the context of other relevant treatments for childhood asthma, we refer to several recently published Cochrane reviews (Adams 1999; Arnold 2008; Guevara 2006; Gøtzsche 2008; Manning 2008; Seddon 2006; Sridhar 2006).

The possibility of publication bias could be further explored by trying to obtain information about studies that have been performed but were never published. However, since most studies we traced were published more than 20 years ago, and expecting unpublished studies to be at least as old, this does not appear to be a very promising endeavour.

This review only addressed DSCG as maintenance therapy in childhood asthma. Other studies have investigated the role of DSCG in attenuating exercise-induced bronchoconstriction, but we are unaware of a systematic review comparing DSCG to placebo for this condition. Indirect evidence from two systematic reviews in this area suggests that DSCG may be beneficial in both adults and children (Kelly 2003; Spooner 2003).

AUTHORS’ CONCLUSIONS

Implications for practice

A considerable number of trials has been performed. Together, they show heterogeneous effects for DSCG compared to placebo as maintenance therapy for childhood asthma. Given the strong indication of publication bias, the small overall treatment effect, and the pooled confidence intervals including zero for our primary outcome measure and several others, we conclude that it is not justified to recommend DSCG as first line maintenance therapy in childhood asthma. This recommendation is further supported by the availability of alternatives with proven effectiveness, i.e. inhaled corticosteroids. For mild persistent asthma evidence is only available for children below the age of four. For this subgroup, there is no good evidence that DSCG is much more effective than placebo. We cannot rule out the possibility that DSCG is of benefit in older children.

Implications for research

Given the place of DSCG in current guidelines, the lack of studies in children from age four onwards with mild persistent asthma is surprising. A large parallel study in this group, of high methodological quality and extended follow up (at least six months), could fill this gap. Preferably, such a study should not only compare DSCG to placebo, but also contain a study arm with low dose inhaled steroids. As the primary outcome measure we would recommend symptoms, either as a symptom score or as a percentage of symptom-free days. Given ongoing concern about the side effects of inhaled steroids, such a study should also address secondary outcomes like growth, adrenal function and bone density. Leukotriene-modifying drugs would be another class of drugs that could be compared to DSCG.

ACKNOWLEDGEMENTS

We are grateful to the following people for:

- searching literature databases: Louis Volkers (Erasmus MC), Karen Blackhall, Liz Arnold (Cochrane Airways Group);
- tracing papers: Philippa Mills (Cochrane Airways Group);
- providing studies: Rhone-Poulenc-Rorer, formerly Fisons plc, Loughborough, UK (Ivo Knottnerus), Alan Edwards;
- their help in translating papers from foreign languages: Toby Lasserson (Cochrane Airways Group, coordination), Keiji Hayashi and Meg Meguro (Japanese), Helena Varonen (Finnish), Diego Martínez de la Concha (Spanish), Dan Peretianu (Romanian), Luca Richeldi (Italian), Vasily Vlassov (Russian), Charlotte Pisinger (Czech), Translingua Rotterdam;
- scoring the methodological quality of our own trial: Sita Bierma-Zeinstra;
- statistical advice: Theo Stijnen, Nico Nagelkerke;
- providing feedback on the synopsis: Alison Whitton.
Inhaled sodium cromoglycate for asthma in children (Review)

References to studies included in this review

Bertelsen 1986 [published data only]

Cogswell 1985 [published data only]

Collins 1971 [published data only]

Dalene 1977 [published data only]

Easton 1973 [published data only]

Edmunds 1980 [published data only]
Edmunds AT, Carswell F, Robinson P, Hughes AO. Controlled trial of cromoglycate and slow-release aminophylline in perennial childhood asthma. *British Medical Journal* 1980;281(6244):842. MEDLINE: 6775752

Furfaro 1994 [published data only]

Geller 1982 [published data only]

Geller 1983 [published data only]

Glass 1981 [published data only]

Henry 1984 [published data only]

Hiller 1975 [published data only]

Hiller 1977 [published data only]

Hyde 1970 [published data only]

Kobayashi 1970 [published data only]

Limborg 1971 [published data only]

Matthew 1977 [published data only]

Mikawa 1986 [published data only]

Shioda 1970 [published data only]

Smith 1970 [published data only]
Inhaled sodium cromoglycate for asthma in children (Review)

References to studies excluded from this review

Anonymous 1969 (published data only)

Avital 1991 (published data only)

Berman 1975 (published data only)

Bernstein 1972 (published data only)

Blumenthal 1988 (published data only)

Bonifazi 1985 (published data only)

Booij-Noord 1971 (published data only)
Booij-Noord H, Orie NGM, de Vries K. Immediate and late bronchial obstructive reactions to inhalation of house dust and protective effects of disodium cromoglycate and prednisolone. Journal of Allergy and Clinical Immunology 1971;48(6):344–54. MEDLINE: 5000940

Bruderman 1990 (published data only)

Carrasco 1989 (published data only)
Carrasco E, Sebulveda R. Comparison of 1 mg and 5 mg sodium cromoglycate metered dose inhalers in the treatment of asthma: a 12-week double-blind, parallel group trial. Current Medical Research and Opinion 1989;11(6):341–53. MEDLINE: 2495900

Carrà 2001 (published data only)

Chai 1973 (published data only)
Chai H. The long-term efficacy and safety of Intal therapy in asthmatic children. In: Pepys J, Yamamura Y editor (s). Intal in Bronchial Asthma. Papers presented at the 8th
Inhaled sodium cromoglycate for asthma in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chan-Yeung 1974a [published data only]

Ciszek 1974 [published data only]

Crawford 1974 [published data only]

Crawford 1974b [published data only]

Crimi 1988 [published data only]

Crisp 1974 [published data only]

Croce 1995 [published data only]

De Baets 1998 [published data only]

Dickson 1969 [published data only]

Droszcz 1973 [published data only]
Droszcz W, Madalinska M. Clinical evaluation of Intal in the treatment of atopic bronchial asthma (double-blind study) [Kliniczna ocena intalu w leczeniu atopowej astmy oskrzelowej] [Podw ojna slepia proba]. *Polskie Archiwum Medycyny Wewnetrznej* trzeze 1973;50:603–6. MEDLINE: 4851656

Edmunds 1994 [published data only]

Engström 1974 [published data only]

Engström 1977 [published data only]

Exline 1972 [published data only]

Forster 1998 [published data only]

Fox 1972 [published data only]

Friday 1973 [published data only]

Fuleihan 1973 [published data only]

Furukawa 1999 [published data only]

Garcia Velloso 1984 [published data only]
Garcia Velloso MA, Maresca OD, Marzorati EH, Perez DL, Pellegrini HMM, Vit E, et al. Controlled trial with cromoglycate in the bronchial asthma [Ensayo controlado...

**Gaur 1997** [published data only]


**Geller-Bernstein 198** [published data only]


**Gemicioglu 1993** [published data only]


**Glazer 1971** [published data only]

Glazer I, Racz I, Molho M. Double blind single crossover clinical evaluation of disodium cromoglicate in bronchial asthma. *International Archives of Allergy and Applied Immunology* 1971;41(1):161–2.

**Godfrey 1975** [published data only]


**Gomez-Orozco 1976** [published data only]


**Graber 1998** [published data only]


**Grifoni 1971** [published data only]


**Gulyas 1984** [published data only]


**Guminiski 1976** [published data only]


**Haber 1989** [published data only]


**Herjavecz 1982** [published data only]


**Hermance 1973** [published data only]


**Hobday 1970** [published data only]


**Hyde 1971** [published data only]


**Hyde 1973** [published data only]


**Inoue 1970** [published data only]


**Irani 1972** [published data only]


**Ito 1971** [published data only]


**Jenssen 1973** [published data only]

Jenssen AO. Disodium cromoglycate (Lomudal) as a prophylactic agent in allergen-induced asthma [Dinatriumkromoglykat (Lomudal) som prophylaktikum ved allergenprovosert astma]. *Tidsskrift for den Norske Laegeforening* 1973;93:17–20. MEDLINE: 4632373

**Johannessen 1975** [published data only]

Johannessen H. The efficiency of hyposensitization and disodium cromoglycate (Lomudal) in bronchial asthma
Inhaled sodium cromoglycate for asthma in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kidner 1968 (published data only)
Kidner PH, Meisner P, Pride NB, Bruce Pearson RS. Treatment of asthma with Intal (disodium cromoglycate) [Wyniki leczenia dychawicy oskrzelowej intalem (disodium cromoglycicum)]. Polskie archiwum medycyny wewn trznej 1974;38:79–83. MEDLINE: 4211720

Klein 1980 (published data only)

Klein 1981 (published data only)

Knezevic 1997 (published data only)

Kotaniemi 2005 (published data only)

Kraemer 1986 (published data only)

Kraemer 1987 (published data only)

Kuzenko 1974 (published data only)

Kuzenko 1977 (published data only)

König 1973 (published data only)

Lahoz 1973 (published data only)

Lecka 1974 (published data only)

Lenney 1978 (published data only)

Linehan 1970 (published data only)
Löwhagen 1985 [published data only]  
Löwhagen O, Rak S. Modification of bronchial hyperreactivity after treatment with sodium cromoglycate during pollen season. *Journal of Allergy and Clinical Immunology* 1985;75(4):460–7. MEDLINE: 3920301

Macdonald 1979 [published data only]  
Macdonald TH, McWilliam R. Monitoring response to bronchodilator therapy in asthma in childhood. *Journal of International Medical Research* 1979;7(suppl 1):87–92. MEDLINE: 108152

Mahashur 1981 [published data only]  

Marks 1974 [published data only]  

Marshall 1969 [published data only]  

Masood 1978 [published data only]  

Matsumoto 1994 [published data only]  

Mattoli 1986 [published data only]  

McLean 1973 [published data only]  

Mellon 1982 [published data only]  

Menardo 1998 [published data only]  

Miraglia 1981 [published data only]  

Miraglia 1982 [published data only]  

Mitchell 1976 [published data only]  

Moeller 2009 [published data only]  

Molema 1989 [published data only]  

Moran 1968 [published data only]  

Muittari 1969 [published data only]  
Muittari A. Prevention of the bronchial obstruction induced by inhalation allergy with disodium cromoglycate [Natriumkromoglykaatti inhalatioallergeenin auheuttaman bronkosuostroksen ehkäisemisä]. *Duodecim* 1969;85:1493–7. MEDLINE: 4907626

Munro Ford 1969 [published data only]  

Naganathan 1975 [published data only]  

Ng 1977 [published data only]  
Inhaled sodium cromoglycate for asthma in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Orefice 1990 [published data only]

Pesic 1975 [published data only]

Price 1995 [published data only]

Rauber 1983 [published data only]

Reid 1988 [published data only]

Robertson 1969 [published data only]

Romano 1970 [published data only]

Sarlet 1973 [published data only]

Schmidt 1973 [published data only]

Selcow 1983 [published data only]

Selcow 1989 [published data only]

Shiota 1984 [published data only]

Shore 1971 [published data only]

Sienra Monge 1990 [published data only]

Silverman 1972 [published data only]

Sly 1970 [published data only]

Smith 1968 [published data only]
Inhaled sodium cromoglycate for asthma in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.


Smith 1980 [published data only]


So 1981 [published data only]

So SY, Yu DYC. Sodium cromoglycate delivered by pressurized aerosol in the treatment of asthma. Clinical Allergy 1981;11:479–82. MEDLINE: 6797755

Streumer 1970 [published data only]


Thompson 1974 [published data only]

Thompson HC, Cochran HD. Use of cromolyn sodium in childhood asthma. Arizona Medicine 1974;31:501–4. MEDLINE: 4208868

Toshner 1974 [published data only]


Turpeinen 2010 [published data only]


Varsano 1983 [published data only]


Viscardi 1997 [published data only]


Watanabe 1992 [published data only]


Weinbren 1969 [published data only]


Wells 1979 [published data only]


Wheatley 1981 [published data only]


Zarkovic 1991 [published data only]


Additional references

Adams 1999


Arnold 2008


BAG 1997


Becker 2005


Berman 1983


BTS 2003


Calpin 1997

Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in
childhood asthma: a systematic review of the literature. *Journal of Allergy and Clinical Immunology* 1997;100:452–7.

**Carlsen 1996**

**Chalmers 1981**

**Church 1985**

**Dersimonian 1986**

**Dickersin 1994**

**Dykes 1974**

**Edwards 1994**

**Egger 1995**

**Egger 1997**

**Elbourne 2002**

**Ernst 1996**

**Fleiss 1993**

**Follman 1999**

**GINA 2005**

**Greenwood 1999**

**Guevara 2006**

**Gotzsche 2008**
Gotzsche PC, Johansen HK. House dust mite control measures for asthma. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [Art. No.: CD001187. DOI: 10.1002/14651858.CD001187.pub3]

**Higgins 2008**

**Hoag 1991**

**Holgate 1996**

**Jadad 1996**

**Kelly 2003**

**Kuzemko 1989**

**Lester 1997**
Leynadier 1985

Manning 2008

Nagelkerke 1992

NIH 1997

NIH 2002

Schweitzer 1994

Seddon 2006

Shapiro 1985

Sharek 1999

Sly 1997

Spooner 2003

Sridhar 2006

Storms 2005

Tasche 2001
Tasche MJA, Uijen JHJM, Bernsen RMD, de Jongste JC, van der Wouden JC. Re: Sodium cromoglycate in childhood asthma (Authors’ reply). *Thorax* 2001;56:331–2.

van Houwelingen 1995

References to other published versions of this review

Tasche 2000

van der Wouden 2003

* Indicates the major publication for the study
### Characteristics of included studies  
*ordered by study ID*

**Bertelsen 1986**

| Methods | DESIGN Parallel-group  
|---------|-------------------------|  
|         | METHODOLOGICAL QUALITY Chalmers score 31/95; Jadad score 3  
|         | WITHDRAWALS/ DROOUTS 5  
|         |  
| Participants | SETTING Hospital outpatients?  
|              | AGE 1 to 4 years  
|              | INCLUSION CRITERIA Recurrent wheezy bronchitis demanding treatment at least once a month during preceding winter or later  
|              | N = 59  
|         |  
| Interventions | 4 to 8 weeks baseline  
|              | 10 weeks treatment  
|              | 3 dd 20 mg  
|              | Nebulised  
|         |  
| Outcomes | Day wheezing  
|          | Day cough  
|          | Sleep disturbance  
|          | Bronchodilator use  
|          | Hospital admissions  
|         |  
| Notes |  

### Risk of bias

| Bias | Authors’ judgement | Support for judgement  
|------|--------------------|------------------------|  
| Adequate sequence generation? | Unclear risk | Not mentioned  
| Allocation concealment? | Unclear risk | Not mentioned  
| Blinding?  
| All outcomes | Low risk | Quote: ‘double-blind’  
| Incomplete outcome data addressed?  
| All outcomes | Low risk | 10 weeks: 5/59 missing, reasons provided, well balanced across groups  
| Free of selective reporting? | Unclear risk | Protocol not available  
| Free of other bias? | Unclear risk | Unclear  

---

*Inhaled sodium cromoglycate for asthma in children (Review)*  
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Cogswell 1985

| Methods | DESIGN Cross-over  
| METHODOLOGICAL QUALITY Chalmers score 43/91; Jadad score 4  
| WITHDRAWALS/ DROPOUTS 3 |
| Participants | SETTING Hospital outpatients?  
| AGE 1 to 4 years  
| INCLUSION CRITERIA Regular attacks of asthma that required at least one admission to hospital  
| N = 27 |
| Interventions | 4 weeks baseline, 2 x 26 weeks cross-over treatment  
| 4 dd 20 mg nebulised |
| Outcomes | % Symptom-free days  
| Day cough  
| Day wheeze  
| Day activity  
| Night cough  
| Overall asthma severity |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>Quote: ‘packaged in identical ampoules’</td>
</tr>
</tbody>
</table>
| Blinding?  
| All outcomes | Low risk | Quote: ‘double-blind’ and ‘identical ampoules’ |
| Incomplete outcome data addressed?  
| All outcomes | Low risk | 24/27 analysed, reasons for withdrawal provided, seems unbiased |
| Free of selective reporting? | High risk | Protocol not available, choice of one outcome (symptom free days) seems post-hoc (see Discussion) |
| Free of other bias? | Unclear risk | unclear |
### Collins 1971

**Methods**
- DESIGN: Cross-over
- METHODOLOGICAL QUALITY: Chalmers score 39/94; Jadad score 2
- WITHDRAWALS/ DROPOUTS: 0

**Participants**
- SETTING: Hospital outpatients?
- AGE: 7 to 17 years
- INCLUSION CRITERIA: Severe allergic asthma, wheeze at least once a week
- N = 14

**Interventions**
- 2 weeks baseline
- 2 x 4 weeks cross-over treatment
- 4 dd 20 mg Spinhaler

**Outcomes**
- Daily symptom scores
- Clinical assessment
- Lung function

**Notes**
- Nr. of patients differs from previous version of review, due to patients on steroids
- Study provided no data for meta-analysis due to incomplete reporting

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>Quote: ‘identical’ and ‘coded by manufacturer’</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Low risk</td>
<td>Quote: ‘double-blind’ ‘physicians nor parents’</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>Apparently no missing data</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>High risk</td>
<td>No results of hemograms, BUN and SGOT</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Dalene 1977

**Methods**
- DESIGN: Cross-over
- METHODOLOGICAL QUALITY: Chalmers score 32/91; Jadad score 3
- WITHDRAWALS/ DROPOUTS: 2

**Participants**
- SETTING: Hospital outpatients?
- AGE: 1 to 4 years
- INCLUSION CRITERIA: Repeated episodes of virus induced asthma
- N = 20
### Dalene 1977  (Continued)

| Interventions          | 2 x 10 weeks  
|                        | Cross-over treatment  
|                        | 4 dd 2 ml 1% solution  
|                        | Nebulised  
| Outcomes               | Day cough  
|                        | Day wheeze  
|                        | Auscultation  
| Notes                  |  

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind'</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>High risk</td>
<td>2/20 did not complete, unclear in which group</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Easton 1973

| Methods                           | DESIGN Cross-over  
|                                  | METHODOLOGICAL QUALITY Chalmers score 35/87 = 40%; Jadad score 2  
|                                  | WITHDRAWALS/ DROPOUTS 0  
| Participants                      | SETTING Hospital outpatients?  
|                                  | AGE Children of unspecified age  
|                                  | INCLUSION CRITERIA Daily extrinsic asthma, stable symptoms, total blood eosinophil counts > 500 cells/cu mm  
|                                  | N = 25  
| Interventions                    | Baseline period unspecified  
|                                  | 2 x 3 weeks cross-over treatment  
|                                  | 4 dd 20 mg capsule  
| Outcomes                          | Total eosinophil count  

*Inhaled sodium cromoglycate for asthma in children (Review)*

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Easton 1973**  
(Continued)

<table>
<thead>
<tr>
<th><strong>Risk of bias</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bias</strong></td>
</tr>
<tr>
<td>Adequate sequence generation?</td>
</tr>
<tr>
<td>Allocation concealment?</td>
</tr>
<tr>
<td>Blinding?</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
</tr>
<tr>
<td>Free of other bias?</td>
</tr>
</tbody>
</table>

**Edmunds 1980**

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>DESIGN Cross-over</td>
</tr>
<tr>
<td>METHODOLOGICAL QUALITY Chalmers score 29/91; Jadad score 2</td>
</tr>
<tr>
<td>WITHDRAWALS/ DROPOUTS 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Participants</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>SETTING Hospital outpatients?</td>
</tr>
<tr>
<td>AGE 5 to 15 years</td>
</tr>
<tr>
<td>INCLUSION CRITERIA Perennial asthma</td>
</tr>
<tr>
<td>N = 30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Interventions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>3 x 4 weeks (incl. additional treatment)</td>
</tr>
<tr>
<td>Cross-over</td>
</tr>
<tr>
<td>4 dd 1 capsule</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Outcomes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
</tr>
<tr>
<td>% Symptom-free days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Notes</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Risk of bias</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bias</strong></td>
</tr>
<tr>
<td>Adequate sequence generation?</td>
</tr>
<tr>
<td>Allocation concealment?</td>
</tr>
</tbody>
</table>
### Edmunds 1980 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Low risk</td>
<td>Table of random numbers</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind'</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear risk</td>
<td>N of results is unclear</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>No details</td>
</tr>
</tbody>
</table>

### Furfaro 1994

<table>
<thead>
<tr>
<th>Methods</th>
<th>DESIGN Parallel-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHODOLOGICAL QUALITY</td>
<td>Chalmers score 56/95; Jadad score 4</td>
</tr>
<tr>
<td>WITHDRAWALS/ DROPOUTS</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>SETTING Outpatients referred to pulmonary clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>0 to 1 years</td>
</tr>
<tr>
<td>INCLUSION CRITERIA</td>
<td>Chronic pulmonary symptoms for at least one month and wheezing documented by a physician + symptoms in baseline period</td>
</tr>
<tr>
<td>N</td>
<td>37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>3 weeks baseline, 6 weeks treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 dd 40 mg nebulised</td>
</tr>
</tbody>
</table>

| Outcomes                     | Symptom score                                    |

| Notes                        |                                                   |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Low risk</td>
<td>Table of random numbers</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind'</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>High risk</td>
<td>3 parental withdrawn, 3 poor compliance, group assignment of these children unclear</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Low risk</td>
<td>Comprehensive listing of outcome measures</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>No details</td>
</tr>
</tbody>
</table>

---

Inhaled sodium cromoglycate for asthma in children (Review)  
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Geller 1982**

**Methods**
- DESIGN Cross-over
- METHODOLOGICAL QUALITY Chalmers score 34/91 = 37%; Jadad score 4
- WITHDRAWALS/ DROPOUTS 5

**Participants**
- SETTING Hospital outpatients?
- AGE 0 to 2 years
- INCLUSION CRITERIA Frequent troublesome wheezy bronchitis despite regular bronchodilator therapy + symptoms in baseline period
- N = 49

**Interventions**
- 2 weeks baseline
- 2 x 4 weeks cross-over treatment
- 4 dd 2 ml nebulised

**Outcomes**
- Symptom score

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind', 'matching placebo'</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>High risk</td>
<td>44/49 analysed, 'one withdrawn while failing to improve during placebo period'</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

**Geller 1983**

**Methods**
- DESIGN Cross-over
- METHODOLOGICAL QUALITY Chalmers score 41/90; Jadad score 4
- WITHDRAWALS/ DROPOUTS 5

**Participants**
- SETTING Hospital outpatients?
- AGE 4 to 13 years
- INCLUSION CRITERIA Moderately severe or severe extrinsic asthma for at least 12 months, not taken DSCG or steroids for at least 6 months before trial
- N = 48

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Geller 1983**  
(Continued)

| Interventions | 2 weeks baseline  
|               | 2 x 6 weeks treatment  
|               | 4 dd 2 mg aerosol  
| Outcomes      | Symptom score  
|               | Asthma severity score  
|               | Lung function  
|               | Patients’, parents’ and physicians’ preferences  
| Notes         |  

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: ‘double-blind’</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>High risk</td>
<td>43/48, 5 withdrawn, ’one failed to improve on placebo’</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

**Glass 1981**

| Methods                              | DESIGN Cross-over  
|                                     | METHODOLOGICAL QUALITY Chalmers score 29/94; Jadad score 2  
|                                     | WITHDRAWALS/ DROPOUTS 0  
| Participants                         | SETTING Hospital outpatients?  
|                                     | AGE 1 to 4 years  
|                                     | INCLUSION CRITERIA Poor control of asthma under routine treatment  
|                                     | N = 16  
| Interventions                        | 4 weeks baseline, 3 x 8 weeks cross-over treatment incl. additional study arm  
|                                     | 4 dd 20 mg nebulised  
| Outcomes                             | Cough  
|                                     | Wheeze  
|                                     | Activity  
|                                     | Sleep disturbance  

*Inhaled sodium cromoglycate for asthma in children (Review)*

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Glass 1981  (Continued)

<table>
<thead>
<tr>
<th>Notes</th>
<th>Additional treatment, Hospital admission Parental preference</th>
</tr>
</thead>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind'</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>High risk</td>
<td>Tables seem to be based on fewer than 16 children (first sentence Results)</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Henry 1984

**Methods**

- DESIGN Cross-over
- METHODOLOGICAL QUALITY Chalmers score 23/94; Jadad score 2
- WITHDRAWALS/ DROPOUTS 3

**Participants**

- SETTING Hospital outpatients?
- AGE 0 to 1 years
- INCLUSION CRITERIA Suffered from recurrent attacks of wheezing, asthma considered troublesome by paediatricians and parents
- N = 23

**Interventions**

- 2 weeks baseline, 3 x 8 weeks cross-over treatment incl. additional study arm
- 3 dd 20 mg nebulised

**Outcomes**

- Wheeze
- Cough
- % Symptom-free days

**Notes**

- Number of withdrawals probably higher
### Henry 1984 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: ‘double-blind’</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear risk</td>
<td>20/23 analysed, unclear whether withdrawal was related to outcome</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>High risk</td>
<td>Biased description of favourable results in some individual patients (p. 56)</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Hiller 1975

| Methods                                       | DESIGN Cross-over  |
|                                               | METHODOLOGICAL QUALITY Chalmers score 44/87; Jadad score 4 |
|                                               | WITHDRAWALS/ DROPOUTS 2 |
| Participants                                  | SETTING Hospital outpatients? |
|                                               | AGE 9 to 13 years |
|                                               | INCLUSION CRITERIA Chronic perennial asthma, symptoms inadequately controlled by DSCG and bronchodilators |
|                                               | N = 11 |
| Interventions                                 | 4 x 1 month cross-over treatment, including 2 additional treatment arms |
|                                               | 4 dd 20 mg Spinhaler |
| Outcomes                                      | Daily symptom scores |
|                                               | Clinical assessment |
|                                               | Additional medication |

### Inhaled sodium cromoglycate for asthma in children (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Hiller 1975  
(*Continued*)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>Quote: 'coded by manufacturers'</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind'</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td></td>
</tr>
</tbody>
</table>

### Hiller 1977

<table>
<thead>
<tr>
<th>Methods</th>
<th>DESIGN Cross-over</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHODOLOGICAL QUALITY</td>
<td>Chalmers score 34/87; Jadad score 3</td>
</tr>
<tr>
<td>WITHDRAWALS/DROPOUTS</td>
<td>0</td>
</tr>
<tr>
<td>Participants</td>
<td>SETTING Hospital outpatients?</td>
</tr>
<tr>
<td></td>
<td>AGE 2 to 4 years</td>
</tr>
<tr>
<td></td>
<td>INCLUSION CRITERIA Frequent troublesome asthma</td>
</tr>
<tr>
<td></td>
<td>N = 17</td>
</tr>
<tr>
<td>Interventions</td>
<td>1 week baseline</td>
</tr>
<tr>
<td></td>
<td>2 x 8 weeks cross-over treatment</td>
</tr>
<tr>
<td></td>
<td>3 dd 20 mg nebulised</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Daily symptoms</td>
</tr>
<tr>
<td></td>
<td>Clinical assessment</td>
</tr>
<tr>
<td></td>
<td>Lung function</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>Quote: 'coded by manufacturers'</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind'</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear risk</td>
<td>All children completed the trial, for 3 children no peak flow</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
</tbody>
</table>

---

Inhaled sodium cromoglycate for asthma in children (Review)  
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Hyde 1970

**Methods**
- DESIGN: Cross-over
- METHODOLOGICAL QUALITY: Chalmers score 38/87; Jadad score 3
- WITHDRAWALS/ DROPOUTS: 3

**Participants**
- SETTING: Hospital outpatients?
- AGE: 6 to 16 years
- INCLUSION CRITERIA: Duration of asthma > 1 year, definite symptoms before inclusion
- N: 60

**Interventions**
- 2 x 3 weeks
- Cross-over treatment
- 4 dd 20 mg Spinhaler

**Outcomes**
- Daily symptom scores
- Clinical assessment
- Lung function
- Additional treatment
- Eosinophil level

**Notes**
- Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>Quote: 'Labels code' (p. 450-1)</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Low risk</td>
<td>Quote: 'double-blind' and taste</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Low risk</td>
<td>57/60 completed, withdrawals due to failure to cooperate or keep adequate records</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Low risk</td>
<td>All outcomes seem to have been addressed</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>unclear</td>
</tr>
</tbody>
</table>
### Kobayashi 1970

**Methods**

- DESIGN: Cross-over
- METHODOLOGICAL QUALITY: Chalmers score 45/90; Jadad score 3
- WITHDRAWALS/DROPOUTS: 7

**Participants**

- SETTING: Hospital outpatients
- AGE: 6 to 15 years
- INCLUSION CRITERIA: Moderate to severe asthma
- N: 37

**Interventions**

- 1 to 2 weeks baseline
- 2 x 4 weeks cross-over treatment
- 3 dd 20 mg Spinhaler

**Outcomes**

- Daily symptom score
- Physician's and patient's impression

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind' and 'code remained unbroken'</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>7/37 withdrawn, seemingly unrelated to outcome</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Limburg 1971

**Methods**

- DESIGN: Cross-over
- METHODOLOGICAL QUALITY: Chalmers score 45/94; Jadad score 3
- WITHDRAWALS/DROPOUTS: 1

**Participants**

- SETTING: Asthma centre, inpatients
- AGE: 6 to 16 years
- INCLUSION CRITERIA: Regular asthma symptoms
- N: 30
**Limburg 1971**  
*(Continued)*

| Interventions | 2 x 4 weeks  
| 4 dd 20 mg Spinhaler |

| Outcomes | Daily symptom scores  
| Lung function  
| Additional treatment  
| Eosinophilia |

| Notes | |

<table>
<thead>
<tr>
<th><strong>Risk of bias</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: ‘double-blind’ and ‘matching placebo’</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>1/30 withdrawn nothing to do with this therapy (p. 368)</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Low risk</td>
<td>All outcomes seem to have been reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>unclear</td>
</tr>
</tbody>
</table>

**Matthew 1977**

| Methods | DESIGN Cross-over  
| METHODOLOGICAL QUALITY Chalmers score 29/87; Jadad score 3  
| WITHDRA WALS/ DROPOUTS 1 |

| Participants | SETTING Hospital outpatients  
| AGE 3 to 6 years  
| INCLUSION CRITERIA Severe chronic perennial asthma + symptoms in baseline period  
| N = 10 |

| Interventions | 8 weeks baseline, 2 x 4 weeks cross-over treatment  
| 4 dd 20 mg nebulised |

| Outcomes | Daily symptom scores  
| Clinical assessment  
| Lung function |

| Notes | |
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding? (All outcomes)</td>
<td>Low risk</td>
<td>‘double-blind’ and ‘placebo identical’</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? (All outcomes)</td>
<td>Unclear risk</td>
<td>Initial number of patients unclear and probably greater than 9 for which data are reported (Nine children completed! p. 36)</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>unclear</td>
</tr>
</tbody>
</table>

### Mikawa 1986

**Methods**
- DESIGN Parallel-group
- METHODOLOGICAL QUALITY Chalmers score 43/92; Jadad score 5
- WITHDRAWALS/DROPOUTS 49

**Participants**
- SETTING Hospital outpatients?
- AGE 6 to 15 years
- INCLUSION CRITERIA Mild to moderate asthma
- N = 196

**Interventions**
- 2 weeks baseline
- 4 weeks treatment
- 4 dd 20 mg aerosol

**Outcomes**
- Symptom scores
- Side effects
- Patients’ and parents’ assessment

**Notes**

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>
### Mikawa 1986  (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Author's judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Low risk</td>
<td>Quote: 'double-blind' and 'neither patients, parents nor clinicians were aware'</td>
</tr>
</tbody>
</table>

### Shioda 1970

<table>
<thead>
<tr>
<th>Methods</th>
<th>DESIGN Cross-over</th>
<th>METHODOLOGICAL QUALITY Chalmers score 42/95; Jadad score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>SETTING Hospital, inpatients and outpatients</td>
<td>AGE 6 to 15 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INCLUSION CRITERIA Perennial asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 34</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 x 4 weeks cross-over treatment</td>
<td>4 dd 20 mg Spinhaler</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Daily symptom scores</td>
<td>Lung function</td>
</tr>
<tr>
<td></td>
<td>Clinical assessment</td>
<td>Additional medication</td>
</tr>
<tr>
<td></td>
<td>School absence</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Author's judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Low risk</td>
<td>Quote: 'double-blind' and 'neither patients, parents nor clinicians were aware'</td>
</tr>
</tbody>
</table>
### Shioda 1970  (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>1/34 withdrawn, unrelated to outcomes (although probably a side-effect)</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>unclear</td>
</tr>
</tbody>
</table>

### Smith 1970

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESIGN Cross-over</td>
</tr>
<tr>
<td>METHODOLOGICAL QUALITY Chalmers score 43/92; Jadad score 4</td>
</tr>
<tr>
<td>WITHDRAWALS/DROPOUTS 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>SETTING Hospital outpatients?</td>
</tr>
<tr>
<td>AGE 7 to 16 years</td>
</tr>
<tr>
<td>INCLUSION CRITERIA Hay fever and pollen asthma confirmed by skin prick tests</td>
</tr>
<tr>
<td>N = 18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
</tr>
<tr>
<td>4 dd 20 mg Spinhaler</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily symptom scores</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Risk of bias</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Low risk</td>
<td>List of random numbers</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind'</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear risk</td>
<td>15/18 completed (368), unclear in which group</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>unclear</td>
</tr>
</tbody>
</table>
### Tischke 1997

#### Methods
- DESIGN Parallel-group
- METHODOLOGICAL QUALITY Chalmers score 75/95; Jadad score 3
- WITHDRAWS/ DROPOUTS 14

#### Participants
- SETTING General practice
- AGE 1 to 4 years
- INCLUSION CRITERIA Previously been prescribed asthma medication and meeting criteria for moderate asthma
- N = 232

#### Interventions
- 4 weeks baseline
- 22 weeks treatment
- 3 dd 10 mg aerosol + spacer (Aerochamber) + face mask

#### Outcomes
- % Symptom-free days
- Daily symptom scores
- Additional medication

#### Notes

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>Quote: ‘treatment allocation was concealed from parents, patients, GPs, research physician and nurses’ (p. 1061)</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: ‘double-blind’</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>167/218 completed study. Equally divided and not related to primary outcome (Fig 1)</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>High risk</td>
<td>All outcome measures seem to be reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>unclear</td>
</tr>
</tbody>
</table>

### Tuchinda 1974

#### Methods
- DESIGN Cross-over
- METHODOLOGICAL QUALITY Chalmers score 49/86; Jadad score 4
- WITHDRAWS/ DROPOUTS 0

#### Participants
- SETTING Hospital outpatients?
- AGE 7 to 12 years
- INCLUSION CRITERIA Chronic asthma
### Tuchinda 1974  (Continued)

<table>
<thead>
<tr>
<th>N = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Quote: 'double-blind', 'identical in taste and color'</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>All patients completed the study</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>No results on symptoms</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Yuksel 1992

<table>
<thead>
<tr>
<th>Methods</th>
<th>DESIGN Cross-over</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>METHODOLOGICAL QUALITY Chalmers score 32/91; Jadad score 2</td>
</tr>
<tr>
<td></td>
<td>WITHDRAWALS/DROPOUTS 0</td>
</tr>
<tr>
<td>Participants</td>
<td>SETTING Hospital outpatients?</td>
</tr>
<tr>
<td></td>
<td>AGE 0 to 2 years</td>
</tr>
<tr>
<td></td>
<td>INCLUSION CRITERIA Preterm born, wheeze and/or cough 3 to 4 days/week for previous 4 weeks + symptoms for at least 3 days following respiratory infections</td>
</tr>
<tr>
<td></td>
<td>N = 16</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 to 3 weeks treatment</td>
</tr>
<tr>
<td></td>
<td>4 dd 5 mg</td>
</tr>
<tr>
<td></td>
<td>Aerosol + face mask (coffee cup)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Daily symptom scores</td>
</tr>
<tr>
<td></td>
<td>Additional treatment</td>
</tr>
<tr>
<td></td>
<td>Lung function</td>
</tr>
</tbody>
</table>
Yuksel 1992  (Continued)

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>‘double-blind’ and ‘similarly shaped and sized cannister’ (Yuksel 1993)</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>All 16 patients completed the study</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Protocol not available, planned outcome measures unknown</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>unclear</td>
</tr>
</tbody>
</table>

Assessment of concealment of allocation for cross-over studies applies only to initial allocation.
Adequacy of washout period not taken into account because of incomplete reports.
Possible unblinding due to perceived differences were not taken into account.
Setting = ? where not clearly stated, but deducted from authors’ affiliations.

dd: doses per day

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agbayani 1984</td>
<td>Double dummy, no placebo arm</td>
</tr>
<tr>
<td>Anastasatu 1979</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Anonymous 1969</td>
<td>Included adults as well, but no age specific results</td>
</tr>
<tr>
<td>Arndt 1975</td>
<td>Not placebo-controlled</td>
</tr>
<tr>
<td>Avital 1991</td>
<td>Theophylline versus placebo (cross-over, double dummy), no placebo arm</td>
</tr>
<tr>
<td>Berman 1975</td>
<td>Partly &gt; 18 years, no separate results for children</td>
</tr>
<tr>
<td>Study</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bernstein 1972</td>
<td>Results for children not presented separately (except patient preference) Continuous use of steroid allowed</td>
</tr>
<tr>
<td>Blumenthal 1988</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Bonifazi 1985</td>
<td>Age 10 to 50, results for children not presented separately</td>
</tr>
<tr>
<td>Booij-Noord 1971</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td></td>
<td>DSCG not as maintenance therapy</td>
</tr>
<tr>
<td>Bruderman 1990</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Carrasco 1989</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Carrà 2001</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Chai 1973</td>
<td>All children on steroids continuously</td>
</tr>
<tr>
<td>Chan-Yeung 1971</td>
<td>Only two children</td>
</tr>
<tr>
<td>Chyrek-Borowska 1975</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Ciszek 1974</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Crawford 1974</td>
<td>Incomplete report</td>
</tr>
<tr>
<td>Crawford 1974b</td>
<td>Most children on steroids continuously (281 doses of 5 mg prescribed in 30 children for 4 weeks)</td>
</tr>
<tr>
<td>Crimi 1988</td>
<td>Not maintenance therapy (adenosine-induced bronchoconstriction)</td>
</tr>
<tr>
<td>Crisp 1974</td>
<td>Steroid use was one of the selection criteria, no separate results for non-users</td>
</tr>
<tr>
<td>Croce 1995</td>
<td>Patients 6 to 24 years</td>
</tr>
<tr>
<td></td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>De Baets 1998</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Dickson 1969</td>
<td>Open study</td>
</tr>
<tr>
<td>Droszcz 1973</td>
<td>Ages 15 to 63 years</td>
</tr>
<tr>
<td></td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Edmunds 1994</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Engström 1975</td>
<td>No placebo for asthma treatment</td>
</tr>
<tr>
<td></td>
<td>Same data as Engström 1977</td>
</tr>
<tr>
<td>Study</td>
<td>Details</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Engström 1977</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Exline 1972</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Forster 1998</td>
<td>Abstract only</td>
</tr>
<tr>
<td>Fox 1972</td>
<td>9 patients were on regular steroids, no separate results for non-users</td>
</tr>
<tr>
<td>Friday 1973</td>
<td>No information on age, included patients above 18 years, no age-specific results</td>
</tr>
<tr>
<td>Fuleihan 1973</td>
<td>Includes both adults and children, no separate results for children</td>
</tr>
<tr>
<td>Furukawa 1999</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Garcia Velloso 1984</td>
<td>No information on age</td>
</tr>
<tr>
<td>Gaur 1997</td>
<td>No information on blinding (possibly not blinded), no placebo</td>
</tr>
<tr>
<td></td>
<td>Results on children not presented separately</td>
</tr>
<tr>
<td>Geller-Bernstein 198</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Gemicioglu 1993</td>
<td>Ages 15 to 46, results for children not presented separately</td>
</tr>
<tr>
<td>Glazer 1971</td>
<td>No information on age</td>
</tr>
<tr>
<td>Godfrey 1975</td>
<td>Study conducted in exercise-induced bronchoconstriction</td>
</tr>
<tr>
<td>Gomez-Orozco 1976</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Graber 1998</td>
<td>Not original, refers to Tasche 1997</td>
</tr>
<tr>
<td>Grifoni 1971</td>
<td>Age 5 to 63 years</td>
</tr>
<tr>
<td></td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Gulyas 1984</td>
<td>Combined therapy, not DSCG alone</td>
</tr>
<tr>
<td>Guminski 1976</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Haber 1989</td>
<td>Patients 16 to 41 years</td>
</tr>
<tr>
<td></td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Herjavecz 1982</td>
<td>No placebo arm</td>
</tr>
<tr>
<td></td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Hermance 1973</td>
<td>Steroid use was continued</td>
</tr>
<tr>
<td>Hobday 1970</td>
<td>No placebo arm (isoprenaline)</td>
</tr>
<tr>
<td>Study</td>
<td>Details</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Hyde 1971</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Hyde 1973</td>
<td>15 of 57 children were on daily steroids</td>
</tr>
<tr>
<td></td>
<td>Results for non-users not presented separately</td>
</tr>
<tr>
<td>Inoue 1970</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Irani 1972</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Ito 1971</td>
<td>only one child below age of 18</td>
</tr>
<tr>
<td>Jenssen 1973</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Johannessen 1975</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Jones 1970</td>
<td>Single-blind</td>
</tr>
<tr>
<td>Kehnscherper 1993</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Kennedy 1969</td>
<td>Primary reference gives no information on age</td>
</tr>
<tr>
<td></td>
<td>Secondary reference gives 10 patients in age range 11 to 20, no specific data</td>
</tr>
<tr>
<td>Khurana 1977</td>
<td>Open study</td>
</tr>
<tr>
<td>Kidner 1968</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Kimmel 1974</td>
<td>Open study</td>
</tr>
<tr>
<td>Klein 1980</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Klein 1981</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Knezevic 1997</td>
<td>(Abstract only)</td>
</tr>
<tr>
<td></td>
<td>No placebo arm</td>
</tr>
<tr>
<td></td>
<td>No information on randomisation</td>
</tr>
<tr>
<td>Kotaniemi 2005</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Kraemer 1986</td>
<td>DSCG single-blind</td>
</tr>
<tr>
<td>Kraemer 1987</td>
<td>Single-blind with respect to SCG</td>
</tr>
<tr>
<td>Kraemer 1993</td>
<td>Daily use of bronchodilator in both arms, irrespective of symptoms</td>
</tr>
<tr>
<td>Kuzemko 1974</td>
<td>Study compares 2 active treatments</td>
</tr>
<tr>
<td></td>
<td>Placebo period not double-blind</td>
</tr>
<tr>
<td>Study Year</td>
<td>Characteristics</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Kuzemko 1977</td>
<td>No placebo</td>
</tr>
</tbody>
</table>
| König 1973  | Not double-blind  
  No placebo period |
<p>| Lahoz 1973  | Adults |
| Leeks 1974  | Included children &gt; 17 years of age, probably above 18 years |
| Lenney 1978 | Exercise induced asthma |
| Linehan 1970 | Single-blind |
| Löwhagen 1985 | Parallel-group trial with only 1 child |
| Macdonald 1979 | Cromoglycate not compared to placebo |
| Mahashur 1981 | Not double-blind, not randomised, no separate results for children |
| Marks 1974  | Incomplete results: only patients who had benefit reported |
| Marshall 1969 | Placebo-controlled study included both children and adults |
| Masood 1978 | Results for children not presented separately |
| Matsumoto 1994 | Not randomised |
| Mattoli 1986 | Allergen-induced challenge |
| McLean 1973  | Included children &gt; 18 years |
| Mellon 1982  | No placebo arm |
| Menardo 1998 | No placebo arm |
| Miraglia 1981 | Not an RCT |
| Miraglia 1982 | 10 of 31 children use steroids continuously, no separate results for non-users |
| Mitchell 1976 | No placebo arm |
| Moeller 2009 | No placebo arm |
| Molema 1989  | Results for children not reported separately |
| Moran 1968   | Results for children not presented separately |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muittari 1969</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Munro Ford 1969</td>
<td>No information on age, probably adults</td>
</tr>
<tr>
<td>Naganathan 1975</td>
<td>37 patients age 11 to 53 years, 6 patients 11 to 20 years, no age-specific results</td>
</tr>
<tr>
<td>Ng 1977</td>
<td>Study compares 2 active treatments&lt;br&gt;Placebo period not double-blind</td>
</tr>
<tr>
<td>Orefice 1990</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Pesic 1975</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Petersen 1996</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Price 1995</td>
<td>Not blinded, no placebo</td>
</tr>
<tr>
<td>Rafinski 1977</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Rauber 1983</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Reid 1988</td>
<td>Results for children not presented separately</td>
</tr>
<tr>
<td>Robertson 1969</td>
<td>Only 1 child</td>
</tr>
<tr>
<td>Romano 1970</td>
<td>No information on ages&lt;br&gt;Description of methods very incomplete&lt;br&gt;No useful results</td>
</tr>
<tr>
<td>Sarlet 1973</td>
<td>Not double-blind&lt;br&gt;No placebo arm</td>
</tr>
<tr>
<td>Schmidt 1973</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Selcow 1983</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Selcow 1989</td>
<td>Age 8 to 20 years&lt;br&gt;Results for children not presented separately</td>
</tr>
<tr>
<td>Sellars 1975</td>
<td>Age of children &gt; 17 years, above 18?</td>
</tr>
<tr>
<td>Shioda 1973</td>
<td>Overlapping data with Shioda 1970, but no data on RCT</td>
</tr>
<tr>
<td>Shiota 1984</td>
<td>Adults only</td>
</tr>
<tr>
<td>Shore 1971</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Sienra Monge 1990</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Silverman 1972</td>
<td>Not placebo-controlled (isoprenaline)</td>
</tr>
<tr>
<td>Sly 1970</td>
<td>2 of 21 children used prednisone continuously, results for non-users not presented separately</td>
</tr>
<tr>
<td>Smith 1968</td>
<td>Not placebo-controlled (isoprenaline)</td>
</tr>
<tr>
<td>Smith 1980</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>So 1981</td>
<td>Aerosol compared to powder, No placebo, Ages 12 to 31</td>
</tr>
<tr>
<td>Streumer 1970</td>
<td>Incomplete description of methods, probably not a RCT</td>
</tr>
<tr>
<td>Thompson 1974</td>
<td>Age 7 to 28 years, Results for children not presented separately</td>
</tr>
<tr>
<td>Toshner 1974</td>
<td>16 patients were on continuous steroids</td>
</tr>
<tr>
<td>Turpeinen 2010</td>
<td>not randomised, no placebo arm</td>
</tr>
<tr>
<td>Varsano 1983</td>
<td>Upper respiratory tract infections, not asthma</td>
</tr>
<tr>
<td>Viscardi 1997</td>
<td>Not asthma</td>
</tr>
<tr>
<td>Watanabe 1992</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Weinbren 1969</td>
<td>Isoprenaline is not placebo</td>
</tr>
<tr>
<td>Wells 1979</td>
<td>Not maintenance therapy, Cat fur challenge</td>
</tr>
<tr>
<td>Wheatley 1981</td>
<td>No placebo arm</td>
</tr>
<tr>
<td>Zarkovic 1991</td>
<td>Open study</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**DATA AND ANALYSES**

This review has no analyses.

**ADDITIONAL TABLES**

Table 1. Methodological quality scores according to Chalmers

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection &amp; reject log</th>
<th>Randomisation &amp; concealment</th>
<th>Blinding</th>
<th>Therap regimens</th>
<th>Withdrawals</th>
<th>Compliance</th>
<th>Numbers &amp; statistics</th>
<th>Timing</th>
<th>Total score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertelsen 1986</td>
<td>1</td>
<td>3</td>
<td>12</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>10</td>
<td>31/95 = 33%</td>
</tr>
<tr>
<td>Cogswell 1985</td>
<td>1</td>
<td>10</td>
<td>13</td>
<td>4</td>
<td>1/3</td>
<td>9/22</td>
<td>2</td>
<td>43/91  = 47%</td>
<td></td>
</tr>
<tr>
<td>Collins 1971</td>
<td>2</td>
<td>7</td>
<td>18</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3/9    = 41%</td>
<td></td>
</tr>
<tr>
<td>Dalene 1977</td>
<td>2</td>
<td>2</td>
<td>16</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>3/20</td>
<td>2      = 35%</td>
<td></td>
</tr>
<tr>
<td>Easton 1973</td>
<td>1</td>
<td>4</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>4/16</td>
<td>3      = 40%</td>
<td></td>
</tr>
<tr>
<td>Edmunds 1980</td>
<td>0</td>
<td>4</td>
<td>14</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>6/20</td>
<td>2      = 33%</td>
<td></td>
</tr>
<tr>
<td>Furfaro 1994</td>
<td>3</td>
<td>13</td>
<td>13</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>11</td>
<td>4      = 59%</td>
<td></td>
</tr>
<tr>
<td>Geller 1982</td>
<td>1</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>6/20</td>
<td>2      = 37%</td>
<td></td>
</tr>
<tr>
<td>Geller 1983</td>
<td>2</td>
<td>6</td>
<td>18</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>5/19</td>
<td>2      = 46%</td>
<td></td>
</tr>
<tr>
<td>Glass 1981</td>
<td>0</td>
<td>4</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>2/9    = 31%</td>
<td></td>
</tr>
<tr>
<td>Henry 1984</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2/9    = 24%</td>
<td></td>
</tr>
<tr>
<td>Hiller 1975</td>
<td>2</td>
<td>10</td>
<td>18</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>5/18</td>
<td>2/9    = 51%</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Methodological quality scores according to Chalmers (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation</th>
<th>Randomisation detail</th>
<th>Double-blind</th>
<th>Blinding details</th>
<th>Withdrawals</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiller 1977</td>
<td>0</td>
<td>10</td>
<td>14</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hyde 1970</td>
<td>1</td>
<td>6</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Kobayashi 1970</td>
<td>2</td>
<td>4</td>
<td>16</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Limburg 1971</td>
<td>1</td>
<td>4</td>
<td>13</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Matthew 1977</td>
<td>0</td>
<td>4</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Mikawa 1986</td>
<td>3</td>
<td>4</td>
<td>16</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Shioda 1970</td>
<td>3</td>
<td>6</td>
<td>18</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Smith 1970</td>
<td>2</td>
<td>4</td>
<td>16</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Tasche 1997</td>
<td>6</td>
<td>11</td>
<td>20</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Tuchinda 1974</td>
<td>1</td>
<td>5</td>
<td>19</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Yuksel 1992</td>
<td>3</td>
<td>4</td>
<td>16</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

/* means denominator adapted because items non-applicable.

Table 2. Methodological quality scores according to Jadad's criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation</th>
<th>Randomisation detail</th>
<th>Double-blind</th>
<th>Blinding details</th>
<th>Withdrawals</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertelsen 1986</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cogswell 1985</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Collins 1971</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dalene 1977</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Easton 1973</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 2. Methodological quality scores according to Jadad's criteria  

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>Imputations from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmunds 1980</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furfaro 1994</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geller 1982</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geller 1983</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass 1981</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henry 1984</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hiller 1975</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hiller 1977</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyde 1970</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kobayashi 1970</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limburg 1971</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matthew 1977</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mikawa 1986</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shioda 1970</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith 1970</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tasche 1970</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuchinda 1974</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuksel 1992</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuksel 1993</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Primary outcome: percentage of symptom-free days

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>Imputations from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cogswell 1985</td>
<td>24</td>
<td>0.34</td>
<td>0.34</td>
<td>11.10</td>
<td>5.10</td>
<td>5.10</td>
<td>0.50</td>
<td>21.70</td>
<td>-</td>
</tr>
</tbody>
</table>

Inhaled sodium cromoglicate for asthma in children (Review)  
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Table 3. Primary outcome: percentage of symptom-free days  
(Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmunds 1980</td>
<td>30</td>
</tr>
<tr>
<td>Henry 1984</td>
<td>20</td>
</tr>
<tr>
<td>Tasche 1997</td>
<td>218</td>
</tr>
</tbody>
</table>

Homogeneity test  
Chi² = 7.48, P = 0.06

Pooled results mean (95% CI)  
Fixed-effect model  
3.57 (-1.18 to 8.32)
Random-effects model  
6.76 (-2.18 to 15.70)

Rho = correlation between DSCG and placebo period (cross-over studies).  
NA = not available in paper.

Table 4. Day cough score

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE from paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>CI Imputations from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertelsen 1986</td>
<td>58</td>
<td>0</td>
<td>0</td>
<td>0.08</td>
<td>0.13</td>
<td>0.13</td>
<td>-0.17</td>
<td>0.33</td>
<td>-</td>
</tr>
<tr>
<td>Cogswell 1985</td>
<td>24</td>
<td>NA</td>
<td>NA</td>
<td>-0.09</td>
<td>0.05</td>
<td>0.05</td>
<td>-0.19</td>
<td>0.01</td>
<td>-</td>
</tr>
<tr>
<td>Dalene 1975</td>
<td>18</td>
<td>NA</td>
<td>NA</td>
<td>-0.12</td>
<td>NA</td>
<td>0.16</td>
<td>-0.44</td>
<td>0.20</td>
<td>Shioda 1970</td>
</tr>
<tr>
<td>Geller 1982</td>
<td>44</td>
<td>NA</td>
<td>0.63</td>
<td>-0.14</td>
<td>NA</td>
<td>0.13</td>
<td>-0.40</td>
<td>0.12</td>
<td>Shioda 1970</td>
</tr>
<tr>
<td>Glass 1981</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>-0.09</td>
<td>0.39</td>
<td>0.39</td>
<td>-0.93</td>
<td>0.76</td>
<td>-</td>
</tr>
<tr>
<td>Henry 1984</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>-0.09</td>
<td>NA</td>
<td>0.15</td>
<td>-0.39</td>
<td>0.21</td>
<td>Shioda 1970</td>
</tr>
<tr>
<td>Hiller 1977</td>
<td>17</td>
<td>NA</td>
<td>NA</td>
<td>-0.18</td>
<td>0.08</td>
<td>0.08</td>
<td>-0.34</td>
<td>-0.01</td>
<td>-</td>
</tr>
</tbody>
</table>

Inhaled sodium cromoglicate for asthma in children (Review)  
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Table 4. Day cough score (Continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE from paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>Homogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shioda 1970</td>
<td>33</td>
<td>0.63</td>
<td>0.63</td>
<td>-0.65</td>
<td>0.12</td>
<td>0.12</td>
<td>-0.89</td>
<td>-0.40</td>
<td>Chi² = 23.44, P &lt; 0.001</td>
</tr>
<tr>
<td>Smith 1970</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>-0.45</td>
<td>0.28</td>
<td>0.28</td>
<td>-1.05</td>
<td>0.14</td>
<td>-0.82 (-0.32 to -0.04)</td>
</tr>
</tbody>
</table>

NA = not available in paper.

**Table 5. Day wheeze score**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE from paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>Imputations from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertelsen 1986</td>
<td>58</td>
<td>0</td>
<td>0</td>
<td>0.06</td>
<td>0.12</td>
<td>0.12</td>
<td>-0.17</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Cogswell 1985</td>
<td>24</td>
<td>NA</td>
<td>NA</td>
<td>-0.09</td>
<td>0.05</td>
<td>0.05</td>
<td>-0.21</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Dalene 1975</td>
<td>18</td>
<td>NA</td>
<td>NA</td>
<td>-0.03</td>
<td>NA</td>
<td>0.06</td>
<td>-0.15</td>
<td>0.09</td>
<td>Cogswell 1985</td>
</tr>
<tr>
<td>Geller 1982</td>
<td>44</td>
<td>NA</td>
<td>0.34</td>
<td>-0.25</td>
<td>NA</td>
<td>0.19</td>
<td>-0.63</td>
<td>0.13</td>
<td>Matthew 1977</td>
</tr>
<tr>
<td>Glass 1981</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
<td>0.04</td>
<td>0.04</td>
<td>-0.07</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Henry 1984</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>-0.10</td>
<td>NA</td>
<td>0.06</td>
<td>-0.22</td>
<td>0.02</td>
<td>Cogswell 1985</td>
</tr>
<tr>
<td>Hiller 1977</td>
<td>17</td>
<td>NA</td>
<td>NA</td>
<td>-0.07</td>
<td>NA</td>
<td>0.06</td>
<td>-0.19</td>
<td>0.05</td>
<td>Cogswell 1985</td>
</tr>
<tr>
<td>Matthew 1977</td>
<td>8</td>
<td>0.26</td>
<td>0.26</td>
<td>-0.54</td>
<td>0.18</td>
<td>0.18</td>
<td>-0.94</td>
<td>-0.14</td>
<td></td>
</tr>
<tr>
<td>Smith 1970</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>-0.45</td>
<td>0.16</td>
<td>0.16</td>
<td>-0.82</td>
<td>-0.08</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Day wheeze score  (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE from paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuksel 1993</td>
<td>16</td>
<td>0.34</td>
<td>0.34</td>
<td>-0.31</td>
<td>0.15</td>
<td>0.15</td>
<td>-0.63</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Homogeneity test

Chi² = 23.47, P = 0.01

Pooled results: mean (95% CI)  Random-effects model

-0.11 (-0.19 to -0.03)

NA = not available in paper.

Table 6. Overall symptom/severity score

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE from paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cogswell 1985</td>
<td>24</td>
<td>NA</td>
<td>NA</td>
<td>-0.12</td>
<td>0.05</td>
<td>0.05</td>
<td>-0.22</td>
<td>-0.02</td>
</tr>
<tr>
<td>Edmunds 1980</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>-0.13</td>
<td>0.04</td>
<td>0.04</td>
<td>-0.21</td>
<td>-0.05</td>
</tr>
<tr>
<td>Furfaro 1994</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>0.17</td>
<td>0.22</td>
<td>0.22</td>
<td>-0.28</td>
<td>0.62</td>
</tr>
<tr>
<td>Geller 1982</td>
<td>44</td>
<td>NA</td>
<td>0.70</td>
<td>-0.20</td>
<td>NA</td>
<td>0.13</td>
<td>-0.46</td>
<td>0.06</td>
</tr>
<tr>
<td>Geller 1983</td>
<td>46</td>
<td>NA</td>
<td>NA</td>
<td>-0.45</td>
<td>0.19</td>
<td>0.19</td>
<td>-0.83</td>
<td>-0.07</td>
</tr>
<tr>
<td>Henry 1984</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>-0.10</td>
<td>NA</td>
<td>0.14</td>
<td>-0.38</td>
<td>0.18</td>
</tr>
<tr>
<td>Hiller 1975</td>
<td>9</td>
<td>NA</td>
<td>NA</td>
<td>-0.24</td>
<td>0.05</td>
<td>0.05</td>
<td>-0.35</td>
<td>-0.13</td>
</tr>
<tr>
<td>Limburg 1971</td>
<td>27</td>
<td>0.67</td>
<td>0.67</td>
<td>-0.18</td>
<td>0.07</td>
<td>0.07</td>
<td>-0.34</td>
<td>-0.03</td>
</tr>
<tr>
<td>Shioda 1970</td>
<td>33</td>
<td>0.70</td>
<td>0.70</td>
<td>-0.94</td>
<td>0.11</td>
<td>0.11</td>
<td>-1.17</td>
<td>-0.70</td>
</tr>
<tr>
<td>Tasche 1997</td>
<td>218</td>
<td>0</td>
<td>0</td>
<td>0.01</td>
<td>0.05</td>
<td>0.05</td>
<td>-0.09</td>
<td>0.11</td>
</tr>
</tbody>
</table>
Table 6. Overall symptom/severity score  (Continued)

<table>
<thead>
<tr>
<th>Homogeneity test</th>
<th>Pooled results: mean (95% CI)</th>
<th>Random-effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi$^2 = 70.76$, P &lt; 0.001</td>
<td>-0.22 (-0.34 to -0.09)</td>
</tr>
</tbody>
</table>

NA = not available in paper.

Table 7. Bronchodilator use (number of doses per day)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE from paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>CI Imputations from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertselsen 1986</td>
<td>58</td>
<td>0</td>
<td>0</td>
<td>-0.33</td>
<td>0.20</td>
<td>0.20</td>
<td>-0.73</td>
<td>0.07</td>
<td>-</td>
</tr>
<tr>
<td>Dalene 1977</td>
<td>18</td>
<td>NA</td>
<td>NA</td>
<td>-0.45</td>
<td>NA</td>
<td>0.11</td>
<td>-0.67</td>
<td>-0.23</td>
<td>Shioda 1970</td>
</tr>
<tr>
<td>Edmunds 1980</td>
<td>30</td>
<td>0.50</td>
<td>0.50</td>
<td>-0.29</td>
<td>0.08</td>
<td>0.08</td>
<td>-0.45</td>
<td>-0.13</td>
<td>-</td>
</tr>
<tr>
<td>Glass 1981</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>0.05</td>
<td>0.04</td>
<td>0.04</td>
<td>-0.04</td>
<td>0.14</td>
<td>-</td>
</tr>
<tr>
<td>Henry 1984</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>0.04</td>
<td>NA</td>
<td>0.10</td>
<td>-0.16</td>
<td>0.24</td>
<td>Shioda 1970</td>
</tr>
<tr>
<td>Kobayashi 1970</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
<td>-0.20</td>
<td>0.09</td>
<td>0.09</td>
<td>-0.40</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>Matthew 1977</td>
<td>25</td>
<td>0.92</td>
<td>0.92</td>
<td>-0.64</td>
<td>0.16</td>
<td>0.16</td>
<td>-1.01</td>
<td>-0.27</td>
<td>-</td>
</tr>
<tr>
<td>Shioda 1970</td>
<td>33</td>
<td>0.79</td>
<td>0.79</td>
<td>-0.75</td>
<td>0.08</td>
<td>0.08</td>
<td>-0.91</td>
<td>-0.59</td>
<td>-</td>
</tr>
<tr>
<td>Smith 1970</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>-0.02</td>
<td>0.05</td>
<td>0.05</td>
<td>-0.13</td>
<td>0.10</td>
<td>-</td>
</tr>
<tr>
<td>Tasche 1997</td>
<td>218</td>
<td>0</td>
<td>0</td>
<td>0.01</td>
<td>0.07</td>
<td>0.07</td>
<td>-0.13</td>
<td>0.16</td>
<td>-</td>
</tr>
</tbody>
</table>

| Homogeneity test | Chi$^2 = 116.06$, P < 0.001 |

Inhaled sodium cromoglycate for asthma in children (Review)
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Table 7. Bronchodilator use (number of doses per day)  

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho paper</th>
<th>Rho paper or imputed</th>
<th>Diff (c-p)</th>
<th>SE paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>Imputations from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass 1981</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>-4.96</td>
<td>8.14</td>
<td>8.14</td>
<td>-20.91</td>
<td>11.00</td>
<td>-</td>
</tr>
<tr>
<td>Hyde 1970</td>
<td>42</td>
<td>NA</td>
<td>NA</td>
<td>-0.69</td>
<td>0.88</td>
<td>0.88</td>
<td>-2.41</td>
<td>1.03</td>
<td>-</td>
</tr>
<tr>
<td>Kobayashi 1970</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
<td>-3.91</td>
<td>6.63</td>
<td>6.63</td>
<td>-16.90</td>
<td>9.08</td>
<td>-</td>
</tr>
<tr>
<td>Limburg 1971</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
<td>-3.61</td>
<td>5.66</td>
<td>5.66</td>
<td>-14.70</td>
<td>7.48</td>
<td>-</td>
</tr>
<tr>
<td>Shioda 1970</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
<td>-1.95</td>
<td>0.87</td>
<td>0.87</td>
<td>-3.66</td>
<td>-0.24</td>
<td>-</td>
</tr>
<tr>
<td>Smith 1970</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>-5.40</td>
<td>12.92</td>
<td>12.92</td>
<td>-30.72</td>
<td>19.92</td>
<td>-</td>
</tr>
<tr>
<td>Tasche 1997</td>
<td>218</td>
<td>0</td>
<td>0</td>
<td>-0.17</td>
<td>0.39</td>
<td>0.39</td>
<td>-0.93</td>
<td>0.59</td>
<td>-</td>
</tr>
</tbody>
</table>

Combining parallel studies (Smith and Tasche)

<table>
<thead>
<tr>
<th>Homogeneity test</th>
<th>Chi² = 0.57, P = 0.45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-effect model</td>
<td>-0.27 (-1.09 to 0.54)</td>
</tr>
<tr>
<td>Random-effects model</td>
<td>-0.27 (-1.09 to 0.54)</td>
</tr>
<tr>
<td>All models</td>
<td>0.76 (0.34 to 1.72)</td>
</tr>
</tbody>
</table>

NA = not available in paper.

Table 8. Steroid use (ln (OR steroid) DCSG/placebo)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho paper from</th>
<th>Rho paper or imputed</th>
<th>Diff (c-p)</th>
<th>SE paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>Imputations from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass 1981</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>-4.96</td>
<td>8.14</td>
<td>8.14</td>
<td>-20.91</td>
<td>11.00</td>
<td>-</td>
</tr>
<tr>
<td>Hyde 1970</td>
<td>42</td>
<td>NA</td>
<td>NA</td>
<td>-0.69</td>
<td>0.88</td>
<td>0.88</td>
<td>-2.41</td>
<td>1.03</td>
<td>-</td>
</tr>
<tr>
<td>Kobayashi 1970</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
<td>-3.91</td>
<td>6.63</td>
<td>6.63</td>
<td>-16.90</td>
<td>9.08</td>
<td>-</td>
</tr>
<tr>
<td>Limburg 1971</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
<td>-3.61</td>
<td>5.66</td>
<td>5.66</td>
<td>-14.70</td>
<td>7.48</td>
<td>-</td>
</tr>
<tr>
<td>Shioda 1970</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
<td>-1.95</td>
<td>0.87</td>
<td>0.87</td>
<td>-3.66</td>
<td>-0.24</td>
<td>-</td>
</tr>
<tr>
<td>Smith 1970</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>-5.40</td>
<td>12.92</td>
<td>12.92</td>
<td>-30.72</td>
<td>19.92</td>
<td>-</td>
</tr>
<tr>
<td>Tasche 1997</td>
<td>218</td>
<td>0</td>
<td>0</td>
<td>-0.17</td>
<td>0.39</td>
<td>0.39</td>
<td>-0.93</td>
<td>0.59</td>
<td>-</td>
</tr>
</tbody>
</table>

Combining parallel studies (Smith and Tasche)

<table>
<thead>
<tr>
<th>Homogeneity test</th>
<th>Chi² = 0.57, P = 0.45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-effect model</td>
<td>-0.27 (-1.09 to 0.54)</td>
</tr>
<tr>
<td>Random-effects model</td>
<td>-0.27 (-1.09 to 0.54)</td>
</tr>
<tr>
<td>All models</td>
<td>0.76 (0.34 to 1.72)</td>
</tr>
</tbody>
</table>

NA = not available in paper.
Table 9. Hospital admittance (\(\ln (OR\) hospital) DSCG/placebo)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Rho from paper</th>
<th>Rho imputed or paper</th>
<th>Diff (c-p)</th>
<th>SE from paper</th>
<th>SE imputed or paper</th>
<th>95% CI left</th>
<th>95% CI right</th>
<th>CI imputations from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertelsen 1986</td>
<td>58</td>
<td>0</td>
<td>0</td>
<td>-0.07</td>
<td>0.55</td>
<td>0.55</td>
<td>-1.17</td>
<td>1.03</td>
<td>-</td>
</tr>
<tr>
<td>Furfaro 1994</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>-0.07</td>
<td>1.46</td>
<td>1.46</td>
<td>-2.97</td>
<td>2.85</td>
<td>-</td>
</tr>
<tr>
<td>Glass 1981</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>8.14</td>
<td>-20.91</td>
<td>11.00</td>
<td>-</td>
</tr>
</tbody>
</table>

Pooling parallel studies (Bertelsen and Furfaro)

<table>
<thead>
<tr>
<th>Homogeneity test</th>
<th>Chi(^2) = 0, P = 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-effect model</td>
<td>-0.07 (-1.08 to 0.94)</td>
</tr>
<tr>
<td>Random-effects model</td>
<td>-0.07 (-1.08 to 0.94)</td>
</tr>
<tr>
<td>All models</td>
<td>0.93 (0.40 to 2.56)</td>
</tr>
</tbody>
</table>

NA = not available in paper.

Table 10. Side effects reported in included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Side effects DCSG</th>
<th>Side effects placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertelsen 1986</td>
<td>Eczema oral (1) Cough (1)</td>
<td>Cough (3)</td>
</tr>
<tr>
<td>Cogswell 1985</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Collins 1971</td>
<td>Bitter taste (20) Cough (11) Dry mouth (4) Dizziness (2) Nausea (2) Sore throat (0) Headache (2)</td>
<td>Bitter taste (13) Cough (1) Dry mouth (2) Dizziness (0) Nausea (0) Sore throat (1) Headache (0)</td>
</tr>
</tbody>
</table>
Table 10. Side effects reported in included studies  *(Continued)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Side Effects Reported</th>
<th>Study</th>
<th>Side Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalene 1977</td>
<td>Not registered</td>
<td>Easton 1973</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Edmunds 1980</td>
<td>Nausea, vomiting, abdominal pain, headache 5%</td>
<td>Furfaro 1994</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Geller 1982</td>
<td>Not mentioned</td>
<td>Geller 1983</td>
<td>None</td>
</tr>
<tr>
<td>Glass 1981</td>
<td>Well-tolerated</td>
<td>Henry 1984</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Hiller 1975</td>
<td>Not mentioned</td>
<td>Hiller 1977</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Hyde 1970</td>
<td>Duration mild side effect less than 5 minutes&lt;br&gt;Throat irritation (4)&lt;br&gt;Headache (1)&lt;br&gt;Brief coughing (4)&lt;br&gt;Wheezing (2)</td>
<td>Hobbs 1997</td>
<td>Mild side effects (40)&lt;br&gt;Eczema mask (5)&lt;br&gt;Cough after inhalation (9)</td>
</tr>
<tr>
<td>Kobayashi 1970</td>
<td>No side effects</td>
<td>Limburg 1971</td>
<td>Cough (2)</td>
</tr>
<tr>
<td>Matthews 1977</td>
<td>Not mentioned</td>
<td>Matthew 1977</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Mikawa 1986</td>
<td>Mild nausea (1)</td>
<td>Mikawa 1987</td>
<td>Mild nausea (1)&lt;br&gt;Mild sore throat (1)</td>
</tr>
<tr>
<td>Shioda 1970</td>
<td>Mild&lt;br&gt;Perioral dermatitis (3)&lt;br&gt;Headache (1)</td>
<td>Shioda 1970</td>
<td>None</td>
</tr>
<tr>
<td>Smith 1970</td>
<td>Not mentioned</td>
<td>Smith 1970</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Tasche 1997</td>
<td>Mild side effects (40)&lt;br&gt;Eczema mask (5)&lt;br&gt;Cough after inhalation (9)</td>
<td>Tuchinda 1974</td>
<td>No side effect experienced</td>
</tr>
<tr>
<td>Yuksel 1992</td>
<td>Not mentioned</td>
<td>Yuksel 1992</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>
**FEEDBACK**

**Criticism of conclusions and methods**

**Summary**

1. The primary outcome measure, symptom free days is directionally in favour of SCG in 3 of 4 studies. The results are dominated by one study in which we doubt whether the dosage was adequate.
2. Of the 16 secondary outcome measures, 8 were statistically significant in favour of SCG. None were in favour of placebo.
3. Of the 17 outcome measures, 11 are to be found in less than 5 studies. Of the 6 outcome measures that included 5 or more studies, 4 are statistically significantly in favour of SCG. None are in favour of placebo.
4. The presentation of the results is misleading.
5. Three methods of drug delivery are included with a dose range of 1 mg 3 times daily to 40 mg 3 times daily. No account is taken of the consequences of efficacy on this dose range. There is ample evidence that 2 of the delivery systems, pMDI and nebulization may not provide an adequate dose particularly in children below the age of 5 years.
6. The diagnosis of asthma is difficult to make with confidence in children below the age of 5 years. At least half the included studies are in children in this age group. Drug delivery also presents problems in this age group.
7. A number of relevant studies have been excluded. We have identified 16 studies that should have been included. Five were excluded as they apparently included subjects over the age of 17 years. Our examination of the papers shows this either not to be the case or results for subjects below 18 years were presented separately. These studies should have been included. The exclusion of studies due to some children being on regular steroid therapy is not justified in those studies in which the steroid dose was kept fixed. If this exclusion was consistent, 2 further studies should have been excluded. It is doubtful if the exclusion of studies in which a fixed dose of bronchodilator was added to both SCG and placebo treatment arms is justified if this review is considered to be representative of SCG in childhood asthma.

**Reply**

We have replied to most of these criticisms before in response to letters by Edwards et al (2002), commenting on a previous version of our review, published in Thorax. Our conclusions are based on both the fact that the confidence interval that we a priori chose to be our guidance (the tolerance interval) does include 'no effect' for most of the outcome measures as well as the strong suspicion of publication bias, as reflected in the funnel plot.

The fact that the diagnosis of asthma is difficult in young children and drug delivery may pose problems, does not mean that doctors should not treat these children, nor does it mean that investigators should not assess the effectiveness of therapeutic options in this group of children. The protocol of our review was clear in excluding studies that included patients over the age of 17 years. In this update, we excluded the study by Kraemer et al for the reasons suggested by the authors of the criticism.

**Contributors**

Criticism of updated review, 7 July 2010

Summary

The current version of the review addresses many concerns which we submitted as a comment previously. We thank the authors for addressing our comments and producing a clearer presentation of the results of their work.

Our criticisms of this review, the previous review and earlier papers on which they were based relate to the statistical methods used, the presentation of the data, the interpretation of the data and the conclusions drawn. A full account of our criticisms can be found in paper by three of us [1]. This was accompanied by two commentaries by statisticians in the same journal [2,3].

The first Cochrane review concluded that ‘The evidence of the efficacy of sodium cromoglicate (DSCG) over placebo is not proven’. In the latest review, the conclusion is ‘There is insufficient evidence to be sure about the efficacy of (DSCG) over placebo’. This is a justified shift in stance, but still understates the case for DSCG. Although there was no statistically significant difference between DSCG and placebo on the primary outcome (symptom-free days), seven secondary outcome variables for which data were available in four or more studies were, according to the authors, all in favour of DSCG, and six were statistically significant. Rather than providing ‘conflicting evidence regarding the superiority of DSCG over placebo’ we believe the review provides overwhelming evidence for the efficacy of DSCG compared to placebo. We do not believe that the authors have fully justified their choice of the primary outcome, given the low power of the of this outcome in that only four studies were included, and one study dominated these results. In one of the commentaries to our paper the author states ‘it seems inappropriate to put major emphasis on the meta-analysis of a primary outcome that is reported in very few of the trials’ [3] They have also not provided an evidence-based response to the criticism that the dose used in this study was probably inadequate.

The authors claim that there may be publication bias, yet this is only weakly supported by their funnel plots which are potentially subject to criticism as they include different outcome variables.

The size of the overall treatment effect is claimed to be small but should be viewed in the light of the mild symptoms experienced by the children. On-treatment mean symptom scores, where given, were less than one (on a 0-3 scale) in both DSCG and placebo treatment groups. Given the relatively low margin for improvement, the treatment effects seen are indeed relevant.

Based on the above, it is surprising that the authors conclude that ‘it is not justified to recommend DSCG as first line therapy in childhood asthma’ (the objective was in any case to assess maintenance therapy). The drug has established evidence of safety and efficacy in a wide number of indications, and has a role in both first line and maintenance therapy.

The authors conclude that ‘a clinically relevant effect of DSCG cannot be excluded’. We suggest that this review provides strong support for the beneficial effect of DSCG over placebo in childhood asthma, particularly those over four years of age.

2. Lewis S, Deeks J. Re Sodium Cromoglicate: An Ineffective Drug or Meta-analysis Misused? Pharmaceut. Statist. 2007; 6: 139-140
3. Lewis JA. Comment on sodium cromoglicate: an ineffective drug or meta-analysis misused? by Stevens et al.; Pharmaceut. Statist. 2007; 6: 141-143

Reply

We thank Dr Edwards and colleagues for their continued interest in our review. The points raised in their comment are not new, and we have carefully considered these when updating our review. As we have already clarified in previous replies, changing the primary endpoint of our review due to its infrequent availability relative to other measurements in the studies would violate elementary methodological principles.

Contributors

A M Edwards, M T Stevens, S T Holgate, SD Anderson, JBL Howell.

Declaration of interest: AME was employed by the originators or sodium cromoglicate, Fisons Pharmaceuticals from 1974 to 1995. MTS was employed by Fisons Pharmaceuticals from 1968 to 1996. STH, SDA and JBHL have all conducted clinical trials with inhaled sodium cromoglicate in the past. None have any financial interest or connection with the current manufacturers.

Inhaled sodium cromoglycate for asthma in children (Review)
### WHAT'S NEW

Last assessed as up-to-date: 27 July 2010.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 November 2010</td>
<td>Feedback has been incorporated</td>
<td>Feedback has been received and appended to the review. The authors have responded to the feedback, but there have been no changes made to the review</td>
</tr>
</tbody>
</table>

### HISTORY

Protocol first published: Issue 1, 2001


<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 July 2010</td>
<td>New search has been performed</td>
<td>Literature search re-run, no new included studies found. Two new excluded studies found.</td>
</tr>
<tr>
<td>7 October 2009</td>
<td>New search has been performed</td>
<td>Literature search re-run; no new studies found.</td>
</tr>
<tr>
<td>27 February 2009</td>
<td>Amended</td>
<td>Risk of bias tables completed, copy edited table of included study.</td>
</tr>
<tr>
<td>25 October 2008</td>
<td>New search has been performed</td>
<td>In response to external peer review: Modified overall description of outcomes, not excluding a clinically relevant benefit. Added forest plots based on values provided in Additional tables 3-19, we could not use the forest plots provided in RevMan, as we assumed a t-distribution when calculating confidence intervals for individual studies. Yuksel 1992 and 1993 combined, as these papers refer to the same study.</td>
</tr>
<tr>
<td>30 May 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>19 December 2007</td>
<td>New citation required and conclusions have changed</td>
<td>In response to comments by Edwards et al, one study was excluded (Kraemer (1993)). Searches performed for years 2003-2007 did not reveal any new studies, but did lead to new 'excluded studies'. Paragraph and table added on side effects as reported in included studies. Paragraph 'other reviews' in Discussion was extended. Tolerance intervals for pooled results removed.</td>
</tr>
</tbody>
</table>
Risk of Bias tables added.
Discussion rewritten.

1 November 2007
New search has been performed
Literature search re-run in November 2007

CONTRIBUTIONS OF AUTHORS
JCvdW drafted text of protocol and review.
MJAT, JHJMU and JCvdW searched papers, assessed inclusion criteria and methodological quality.
RMDB and JCvdW extracted data. RMDB performed statistical analysis.
JHJMU and JCvdW drafted the 2008 update.
All authors commented on versions of the protocol and review.

DECLARATIONS OF INTEREST
The authors were involved in a placebo-controlled trial (Tasche 1997) and in an earlier systematic review comparing DSCG and placebo (Tasche 2000). Both studies had negative conclusions.

SOURCES OF SUPPORT

Internal sources
- Department of General Practice, Erasmus MC - University Medical Center Rotterdam, Netherlands.

External sources
- No sources of support supplied

INDEX TERMS
Medical Subject Headings (MeSH)
Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Cromolyn Sodium [*therapeutic use]; Randomized Controlled Trials as Topic
MeSH check words

Child; Humans