Nedocromil sodium for preventing exercise-induced bronchoconstriction (Review)

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TABLE OF CONTENTS

[Intervention Review]

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ABSTRACT

Background

Exercise-induced bronchoconstriction (EIB) following strenuous physical exertion afflicts many people. It can be the cause of sub-optimal performance, symptoms such as cough, dyspnea, wheeze and chest tightness, and can lead people to avoid physical activity. Management of EIB focuses on prevention through pharmacotherapy and alternate strategies. Single use, pre-exercise, beta-agonists and non-steroidal antiinflammatory agents are recommended.

Objectives

Bronchodilator medications have been commonly used to prevent narrowing of airways after exercise, but anti-inflammatory drugs such as nedocromil sodium have also been used. The objective of this review was to assess the effects of a single dose of nedocromil sodium to prevent exercise-induced bronchoconstriction.

Search methods

We searched the Cochrane Airways Group Specialised Regsiter, the Cochrane Central Register of Controlled Trials, Current Contents, review articles, textbooks and reference lists of articles. We also contacted the drug manufacturer and primary authors for additional citations. Searches have been updated to August 2008.

Selection criteria

Randomised trials comparing a single dose of nedocromil sodium with placebo to prevent exercise-induced bronchoconstriction in patients with EIB over six years of age.

Data collection and analysis

Trial quality assessment and data extraction were conducted independently by two reviewers. Study authors were contacted for confirmation of data. No new studies were identified in an update search conducted in August 2008.

Main results

The combined results from 20 randomised controlled trials involving 280 participants, show that 4 mg, of nedocromil sodium inhaled 15 to 60 minutes prior to exercise significantly reduce the severity and duration of EIB in both adults and children, when compared to placebo. The maximum percentage fall in FEV1 was improved significantly compared to placebo (weighted mean difference 15.5 %; 95% confidence interval:13.2 to 18.1). For the maximum percentage fall in peak expiratory flow rate (PEFR) the improvement was similar: WMD 15.0%, (95% CI 8.3 to 21.6). Nedocromil shortened the time to recover lung normal function from more than 30 minutes with placebo to less than 10 minutes with the drug. It had a greater effect on those patients with more severe exercise-induced bronchoconstriction (defined as an exercise-induced fall in lung function > 30% from baseline). There were no significant adverse effects reported with the short term use of nedocromil. A further search conducted in August 2005 did not yield any further studies.

Authors' conclusions

Nedocromil sodium used before exercise reduces the severity and duration of exercise-induced bronchoconstriction. This effect appears to be more pronounced in people with severe exercise-induced bronchoconstriction.

PLAIN LANGUAGE SUMMARY

Nedocromil sodium for preventing exercise-induced bronchoconstriction

Exercise-induced asthma can limit people's endurance, prolong recovery time after exercise, and lead to people avoiding exercise. The episode involves symptoms such as coughing, wheezing, shortness of breath and chest tightness. The review of trials found that nedocromil sodium (Tilade) inhaled 15 to 60 minutes before exercise may reduce the severity and length of this kind of asthma for both adults and children, particularly those who have severe episodes.

BACKGROUND

Transient airway narrowing following strenuous physical exercise is referred to as exercise-induced bronchoconstriction (EIB) and was first described nearly 2000 years ago. It occurs in 70% to 80% of people with asthma (Anderson 1985), 35 to 40% of people with allergic rhinitis (McCarthy 1989) and an estimated 12% to 15% of the general population (Spector 1993). Several studies conducted among athletes indicate that from 3 to 14% suffer EIB (Mehta 1997).

EIB is typically provoked by 6 to 15 minutes of continuous, strenuous exercise of at least 80 to 90% predicted maximum workload (Bar-Yishay 1984). The increase in airway narrowing causes symptoms such as dyspnea, cough, wheeze, and premature fatigue, and results in prolonged recovery times. Maximum bronchoconstriction occurs 5 to 15 minutes after exercise terminates and usually subsides spontaneously within 20 to 60 minutes (Virant 1992). By consensus, post-exercise decreases of 10% to 20% in forced expiratory volume in 1 second (FEV1) or in the peak expiratory flow rate (PEFR) indicate mild EIB; a fall of 20% - 40% represents moderate EIB, and > 40% fall represents severe EIB (Eggleston 1984).

Several factors influence the severity of EIB: concomitant asthma therapy, intensity and duration of activity, environmental conditions, degree of underlying bronchial hyperreactivity, level of physical conditioning, and the time interval since previous exercise (Rupp 1996). Episodes can be severe enough to require rescue medication, even emergency treatment, and thus are a concern not only to those who suffer from it, but also to all those who supervise physical activities. Symptoms caused by EIB can hinder active participation, cause sub-optimal performance on the job or in sports and can affect self-esteem. Considerable expenditures result from the treatment of EIB mainly from health service utilisation and pharmaco-therapy. The benefits of successful management can be remarkable at all ages and levels of activity; for example, with treatment, the athletes with EIB that competed at the 1984 Olympics won 41 medals (Pierson 1988).

The issues relating to the etiology and mechanisms of EIB are complex and some remain unresolved. EIB is stimulated by an increase in minute ventilation that necessitates rapid re-warming and humidification of large volumes of air. A loss of peri-ciliary fluid in the airway lining is thought to create a hyper-osmotic environment

which then activates degranulation of pulmonary mast cells and the subsequent release of inflammatory mediators that cause bronchoconstriction (Anderson 1984). Re-warming may cause vascular engorgement and edema that might also contribute to airway narrowing (McFadden 1986). Management of EIB has focused on prevention through both pharmacologic and non-pharmacologic interventions. Different drugs have been found useful, however, there is considerable debate regarding the merits of each treatment, the optimal dose and the optimal delivery method. Traditionally, inhaled bronchodilators (IBDs) and other bronchodilators (BDs) have been the drugs of choice (Virant 1992; Sly 1984). Recently, anti-inflammatory agents such as NCS, sodium cromoglycate (SCG), and inhaled corticosteroids (ICS) have been investigated, as have antihistamines, furosemide, heparin, calcium-antagonists, theophyllines and leukotriene antagonists.

NCS, a mast cell stabilising agent, was introduced in the 1980's for use in chronic asthma management. It has been reported to be effective on a single dose basis against bronchoconstriction due to antigens, fog, cold air, sulfur dioxide, and exercise (Holgate 1986). This systematic review examines the available evidence on NCS in preventing or attenuating EIB.

OBJECTIVES

The objectives of the review were:

- To identify all randomised controlled trials using NCS to treat reproducible EIB in participants with asthma who were at least 6 years of age. To provide a pooled estimate of the effect of administering a single prophylactic dose of NCS on pulmonary function tests (PFT), using FEV1 and PEFR, following a standard exercise challenge.
- To determine if the dose of NCS, the delivery method, the timing of pre-treatment, the severity of EIB, the age or sex of subject influenced the magnitude of effect.
- To explore the time-course of EIB post exercise.
- To determine other benefits or harms related to nedocromil.

A priori, reviewers planned subgroup analyses based on:

- age (those 17 years and younger were considered children)
- gender
- severity of EIB (a mean maximum % fall in PFT after placebo < 30% was considered milder EIB, 30% and greater was considered moderate - severe EIB)
- dosage NCS given
- delivery system used
- timing of pre-treatment

METHODS

Criteria for considering studies for this review

Types of studies

To be considered for inclusion, clinical studies had to be randomised, placebo-controlled, double-blind trials.

Types of participants

All studies on children and adults who had a history of EIB, or who demonstrated that they had EIB in a 'control' standardised exercise challenge prior to entry into the trial, were considered for inclusion. EIB was defined as a fall in FEV1 or PEFR following exercise of 10% or greater.

Types of interventions

Participants had to be randomised to receive any dose of inhaled NCS or an inert placebo as a single prophylactic treatment prior to undergoing a standardised exercise challenge test. If studies had more than one drug arm, only the comparison of NCS to placebo were included. Studies that involved delivery via nasal sprays were not included.

Types of outcome measures

Both subjective and objective outcomes were considered. The conventional method to quantify EIB is to measure the maximum reduction in FEV1 or PEFR and to express it as a percent (%) fall index, that is, to express the reduction in lung function after exercise as a percent of the pre-exercise value. The effect of drug therapy on bronchoconstriction is also expressed as the degree of protection offered from airway obstruction by the active drug compared to the placebo response (Anderson 1995).
The formula used to calculate the % fall index was:
maximum % fall in FEV1 or PEFR = 100 x (immediate pre-exercise value - lowest post-exercise value) / pre-exercise value
The formula used to calculate the % protection index was:
% protection index = 100 x (maximum % fall FEV1 or PEFR placebo - maximum % fall FEV1 or PEFR NCS) / maximum % fall FEV1 or PEFR placebo

A protection index of 50% or greater is regarded as clinically significant (Anderson 1995).
Primary outcome measures of interest were continuous data reporting:

- mean maximum % fall in FEV1 or PEFR;
- mean % fall in FEV1 at varying time points post-exercise challenge;

- mean % protection afforded by NCS compared to placebo.

Secondary outcomes considered were symptom scores, physiologic measures, performance measures, and adverse effects.

Search methods for identification of studies

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 and CINAHL, and handsearching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' were searched using the following terms:
(physical* OR exercis* OR train* OR fitness OR bronchoconstrict* OR bronchospas* OR EIB OR EIA) AND (nedocromil* OR dscg OR cromo* OR tilade OR intal)

This search is updated annually. The most recent search was carried out in August 2008.
In addition, the Cochrane Central Register of Controlled Trials (CENTRAL), Current Contents, plus reference lists of included studies, review articles and textbooks were searched for relevant citations. The manufacturer of NCS (Rhone-Poulenc Rorer) and the authors of included studies were asked to identify additional published, unpublished or 'in-progress' studies.

Data collection and analysis

Selection of studies

One reviewer performed the initial search of all the databases to identify citations with potential relevance. Two independent reviewers screened these results to exclude articles that were clearly irrelevant, then the full text of remaining articles was retrieved (and translated into English where required). The bibliographies of pertinent articles, reviews and texts were searched for additional citations. Using defined eligibility criteria, two independent reviewers decided on trial inclusion. A priori, reviewers made the decision to exclude any data that was available only in abstract form. Reviewers were not blinded to authors, journal, results, etc. Agreement was measured using kappa statistics. Disagreements were resolved by discussion.

Data extraction and management

Data were independently extracted by two reviewers using a standard form. All numeric calculations and graphic extrapolations were confirmed by a second person. Reviewers attempted to contact all authors (using e-mail, letter and fax) to search for additional papers, confirm data extraction, and to obtain missing data.

Assessment of risk of bias in included studies

Included trials were subjected to two quality assessments by two independent reviewers using two approaches:
1. The Cochrane approach to assessment of allocation concealment:

- Grade A: Adequate concealment
- Grade B: Uncertain
- Grade C: Clearly inadequate concealment

2. A 5 point scoring system described by Jadad (1996) and summarised as follows:

- Was the study described as randomised (1=yes; 0=no)
- Was the study described as double-blind (1=yes; 0=no)
- Was there a description of withdrawals and dropouts (1=yes; 0=no)
- Was the method of randomisation well described and appropriate (1=yes; 0=no)
- Was the method of double blinding well described and appropriate (1=yes; 0=no)

Deduct 1 point if methods for randomisation were inappropriate
Deduct 1 point if methods for blinding were inappropriate

Dealing with missing data

When the standard deviation (SD) for changes in lung function for each treatment was missing from a study, an estimate was imputed. The estimate was based on the weighted average (by sample size) of the deviations from other included studies for that category (i.e. adults, children, FEV1, PEFR). A sensitivity analysis was performed to check the effect of imputation.

Data synthesis

All twenty included studies were small crossover trials (sample size: 8 to 24, mean 14). At the time of this review, debate existed within the Cochrane Collaboration (CC) on how to handle data from crossover trials. Research continues in the area of comparing results on the same patients that is reported as individual patient data, parallel study data, and summary data from crossover trials. In this review the treatment and placebo group data were analysed as though from parallel group studies (CC Handbook 1997). This approach would be expected to yield a more conservative pooled estimate of treatment effect.
The data were entered into the Cochrane Collaboration software program Review Manager 3.0.1. FEV1 and PEFR are continuous measures, the individual and pooled statistics are reported as a weighted mean difference (WMD) of treatment effect with 95% confidence intervals (95% CI) using the random effects model. The data were entered in such a way that when analysing the MetaView graphs, the area to the left of the midline indicates a favourable outcome for NCS. Homogeneity in pooled estimates was tested using chi-square statistics.

To investigate whether treatment with NCS was dependent on the baseline severity of EIB experienced by participants, studies were dichotomised according to the mean maximum % fall in FEV1 or PEFR following placebo treatment in order to account for the placebo response. A priori, mild EIB was defined as a mean maximum % fall in FEV1 or PEFR < 30%, moderate-severe EIB was defined as a mean maximum % fall in FEV1 or PEFR 30% or greater.

Time Course Analysis: Thirteen manuscripts included line graphs that depicted the mean percent change in FEV1 from pre-exercise baseline at 0-1 minute, then at 2-3, 5, 10, 15, 20 and 30 minutes post-exercise, comparing the NCS to placebo response. Reporting of the absolute values with SD's to accompany the graphs were rare, therefore, graphs were enlarged and two independent reviewers estimated the mean percent fall FEV1 values for NCS and placebo groups. Where estimates between reviewers differed, the average of the two was used. The mean and SD for each time point was calculated. The Mann-Whitney test was used to test the significance of the differences at each time point using an alpha of 0.05.

Mean % Protection Index: A protection index was calculated for each study using the formula described earlier. The mean, SD, and 95% CI's among trials was then calculated to provide an aggregate estimate of protection offered by using NCS.

Subgroup analysis and investigation of heterogeneity

Subgroup comparisons are outlined in the Comparisons section. Subgroup analysis by sex and concomitant therapy was not possible due to lack of data.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Forty-seven titles and abstracts were selected from the original database search. Four additional citations were identified from the reference lists of relevant publications for a total of fifty-one potentially relevant studies. From the text in title, abstract, and keywords, two reviewers independently selected 32 (63%) for full text review (kappa 0.92). Two independent reviewers determined that twenty-two trials met the inclusion criteria (kappa 0.75). Further discussion and clarification of the inclusion criteria resulted in 100% agreement for the inclusion of the twenty-two trials. Of the four citations identified from bibliographies, one met the inclusion criteria (Mihalyka 1988). Bauer 1986 was removed because it was the only study to use specific airways resistance measures. Sinclair 1990 did not report mean maximum % fall indices but did report data that was included in the time course results. An update search conducted in August 2008 did not yield any additional studies. Results from 20 studies are included in the meta-analysis.

Included studies

Summary details are given in the 'Characteristics of Included Studies' section and described in general terms below.

DESIGN ISSUES

All studies used the crossover design. Seven trials included a second drug arm: SCG (N = 6), furosemide (N = 1). (N = number of studies reporting data). Including these comparisons was beyond the scope of this review. Unfortunately, only one trial provided the sequence of randomised treatments, which precluded an investigation of 'carry-over' or 'period' effects. A pharmacologic 'carryover' effect was deemed to be unlikely since NCS is a short-acting agent (half life 1.5 - 2 hour), that does not accumulate, and is rapidly cleared from the body (CPS, 1996). A carry-over from the other two drugs was also deemed to be negligible, again because each drug had a short half-life, 80 minutes and 2 hours respectively. The challenges were conducted on separate days and the trialists adhered to the recommended washout time of 5 to 10 times the half-life of a drug (Shapiro 1983).

POPULATIONS

Recruitment procedures were not well described, but it appeared that convenience samples of volunteers predominated. Only one dropout was reported (not included in analysis). Seventeen of the trials were conducted in Europe and the UK. The analysis includes data on 280 participants (179 males, 87 females); one study did not report the number of males and females. 162 (58%) participants were children between the ages of six and 17 years, 104 (42%) were adults aged 18 - 59 years. Each trial required subjects to have a reproducible maximum % fall in FEV1 or PEFR of at least 15% (N =10) or 20% (N = 9). No women who were either pregnant or at risk of being pregnant were included. Two studies included only non-smokers, otherwise smoking history was not mentioned. All subjects were described as being 'stable asthmatics' at the time of challenge testing (lung function > 70% of predicted values, variability between challenges < 10 - 15%). Todaro (1993) studied Olympic level athletes, none of the remaining trialists addressed the subject's level of physical conditioning.

Concomitant therapy included a variety of common anti-asthma agents but most medications were discontinued for periods of 6

hr. to 1 wk. prior to each challenge to effect a washout and to limit a confounding influence.

INTERVENTIONS

Trials evaluated a range of doses of NCS that included 1 mg (N = 1), 2 mg (N = 3), 4 mg (N = 18) and 8 mg (N = 2) given via MDI (5 studies used a spacer device). Timing of administration varied from 15 min (N = 3), 20 min (N = 8), 30 min (N = 8), to 60 min (N = 1) before a standardised exercise challenge of sufficient intensity and duration to induce EIB. All studies conducted the challenges on different days (consecutive days up to 1 week) at the same time of day, but not all studies stated the time of day chosen. The challenges were conducted indoors in controlled environments with temperatures between 17-24 C and relative humidity between 35 - 60%. The Oseid 1995 trial was performed at -18 C in dry air.

OUTCOMES

The two most common outcomes reported were: mean maximum % fall in FEV1 (N = 17) and/or PEFR (N = 7). Thirteen trials recorded the mean % fall in PFT at time points that ranged from cessation of exercise up to 30 minutes. Three trials assessed the duration of treatment effect post-exercise over two or three challenges that were 2 - 4 hours apart, on the same day (Chudry 1987; De Benedictis 1995; Konig 1987].

No outcome data on symptom scores, performance measures, patient preference, or physiologic measures were systematically collected and reported. Twelve of twenty studies (60%) commented on adverse effects. Seven of these (58%), stated that no adverse effects were noticed in the time period that participants were observed.

Risk of bias in included studies

Using the Cochrane criteria to assess allocation concealment, two studies (Chudry 1987; Sinclair 1990) were rated as having "adequate" concealment, all others were given an "unclear" status.

Using Jadad's 5 point validity scale, 2 studies rated 5 (strong), 10 rated 4 (very good), and 12 rated 3 (good). All studies stated they were randomised and double-blinded, all either described dropouts or had none; however, most studies lacked a sufficient description of the method of randomisation and/or blinding used.

Effects of interventions

Pulmonary function

Seventeen trials (N = 11 children, N = 6 adult, total sample size = 240) reported the response to treatment as a change in the mean maximum % fall in FEV1 (max % fall FEV1). When NCS was used, the mean max % fall FEV1 was significantly attenuated immediately post-exercise (WMD: 15.6%; 95% CI: 13.2, 18.1, Analysis 1.1). The chi-square test for heterogeneity was non-significant for the pooled result. The result was not significantly different in subgroup analysis based on the age of subjects, the dose of NCS given, the delivery system used, or the timing of pre-treatment.

Seven trials (N = 4 children, N = 3 adult, total sample size = 115) reported the response to treatment as a change in the mean maximum % fall in PEFR (max % fall PEFR). The pooled estimate from these studies demonstrated NCS significantly attenuated the mean max % fall PEFR in the immediate post-exercise period (WMD: 15.0%; 95%CI: 8.3, 21.6); however, significant heterogeneity in this pooled result was demonstrated (Chi-squared = 20.28, df=6, $p < 0.001$).

Sensitivity analysis based on study quality (Jadad score = 3 versus Jadad scores of 4 & 5), imputed standard deviations (N = 2), random vs fixed effects models and publication status were non-significant and did not address the heterogeneity of the result.

A priori sub-group comparisons based on the age of subjects, the dose of NCS given, the delivery system used, and the timing of pre-treatment did not explain the heterogeneity.

Heterogeneity was not evident when studies were dichotomised into mild EIB/more severe EIB groups (mild EIB, N = 4: Chi-squared 0.31,df 3, $p > 0.20$; more severe EIB, N = 3: Chi-squared 1.64, df 2, $p > 0.20$). This subgroup analysis indicated that NCS inhibited the mean max % fall PEFR in subjects with more severe EIB (WMD: 25.1%; 95% CI: 18.7, 31.1) to a significantly greater degree than in subjects with mild EIB (WMD: 8.3%; 95% CI: 4.1, 12.5).

Similar results were demonstrated for mean max % fall FEV1 results. The WMD: 21.4% (95% CI: 17.2, 25.5) for more severe EIB (N = 8) compared to WMD: 12.8% (95% CI: 10.0, 15.7) for mild EIB (N = 9).

According to the American Thoracic Society (1993) and the Canadian Consensus Guidelines (1996) a 12% change in FEV1 is considered clinically significant.

The protection index is another measure commonly employed and reported in the EIB literature. Inhibition of the maximum drop in the FEV1 or PEFR by the active drug of 50% or more over placebo therapy, is believed to represent a clinically significant difference (Anderson 1995). On average, NCS provided a measure of 51% protection (95% CI: 46, 55) against a decrease in FEV1 over a placebo (SD 9.96, range 31 to 70%). A similar protection index was calculated for PEFR values: 49.2% (95% CI: 40, 58).

A few studies included individual patient data. Further exploration of these data was beyond the scope of this review yet one observation is worthy of mention in light of the discussion of two frequently referenced trials that follows.

Nebulised NCS in known responders

Two studies (Albazzaz 1989; Albazzaz 1992) were excluded from this review because the trialists deliberately selected 'responders' after a control test verified that NCS attenuated the fall in FEV1 by at least 40% in each individual. Together, these trials tested 5 concentrations of nebulised NCS (0.5, 2.5, 5.0, 10, 20 mg/ml) on 20 adult subjects given 15 minutes pre-exercise challenge. Following all doses of NCS subjects experienced a mean max % fall in FEV1 of <15% (range 8.0 to 14.1 %) vs a placebo fall of 29% (range 28 to 31%). Albazzaz (1992), tested the duration of effect and found NCS to provide significant inhibition at both 135 and 255 minutes post treatment. No significant differences in inhibitory effect were noted among different doses but all were significantly better than placebo ($p < 0.001$). These trials suggest that NCS may have a greater effect when only those who are 'responders' are studied.

Dose response

No definite trend in response was noted when comparing trials using low, moderate or high doses of NCS, however, it must be pointed out that the small number of trials using a low dose (2 mg or less, N = 3) or a high dose (> 4 mg, N = 1) prevented any meaningful analyses for a trend in dose-response effect. The recommended clinical dose of 4 mg was used in 16 of 20 studies.

Duration of effect

Three trials, all using the mean max % fall FEV1, provided data on repeated challenges to evaluate NCS for its duration of effect. No significant benefit was demonstrated beyond the first challenge test. The difference in max % fall FEV1 between placebo and NCS groups at 2 to 2.5 hr. was not significant (WMD: 6.0%; 95% CI: 1.0, 12.9; N = 3) nor was there a benefit at 4 to 4.5 hr. (WMD: 5.7%; 95% CI: 2.8, 14.2; N = 2).

Time course analysis

Thirteen studies reported the mean percent changes in FEV1 at seven time points during the post-exercise period (0-1 min, N= 13; 2-3 min, N=13; 5 min, N=13; 10 min, N=13; 15 min, N=12; 20 min, N=10; and 30 min, N=5). Significant group differences that favoured NCS were noted at all times up to 30 minutes post-exercise. The return to normal lung function (i.e. less than a 10% change from baseline) occurred within 10 minutes post-exercise using NCS compared to 30 minutes using placebo.
The results for % fall FEV1 over time are tabulated below:

Time (min)	Nedocromil (mean, SD)		Placebo (mean, SD)		P value
0-1	2.5	5	11.7	8	<0.001
2-3	9.1	7	22.5	11.7	0.002
5	11.3	5.1	26	8.5	<0.001
10	8.8	4	22.6	6.5	<0.001
15	6.2	3.5	18.4	6.4	<0.001
20	3.8	2.9	14.3	6.3	<0.001
30	1.4	1.4	11.1	5.6	<0.008

Side effects

Though data on side effects were not collected systematically, most authors reported no symptoms and no serious adverse effects attributable to NCS. Five studies mentioned minor side effects which included a bad taste, throat irritation and cough (see Table of Included Studies). One study, (Henriksen 1988) reported a mean increase in heart rate after NCS; however, this was not clinically significant (4 beats per minute). Increasing the dose of NCS did not appear to increase the side effects.

DISCUSSION

EIB is a significant clinical problem for which an effective and safe prophylactic treatment is necessary. This systematic review and meta-analysis of 20 randomised, crossover trials on 280 adults and children, across 8 countries, over 10 years, supports the use of a single dose of NCS as a safe and effective pharmaceutical option.

The studies reviewed included participants with stable lung function at the time of testing (> 70% predicted values, < 10 - 15% variability between challenges) and despite a variety of concomitant anti-asthma therapies, each individual demonstrated diagnosable EIB in a control test with a fall in FEV1 or PEFR of at least 15%. NCS treatment significantly inhibited bronchoconstriction by an average 16%, shortened the duration of EIB to less than 10 minutes and provided a clinically significant protection over placebo of 51%. Moreover, this effect was more pronounced in those with more severe EIB. The pooled effect was homogeneous for age, dose, timing of pre-treatment, and delivery method. The latter may be due to the fact that participants had good inhaler technique to begin with and therefore adding a spacer would provide no additional advantage. It did not appear that a protective effect remained in subsequent exercise challenges 2 hr. and 4 hr. after administration of NCS.

NCS was well tolerated, adverse effects were minor complaints of throat irritations, and an unpleasant taste was noted by a few.

Methodological limitations

There are no major issues that would limit the applicability of these results in a similar population but there are a few cautionary notes.

1. The overall findings may be generalised to people who have asthma and atopy with stable lung function yet reproducible EIB when exercising at a level of sufficient intensity and duration. People with EIB caused by other airway disorders were not studied.

2. All of the challenges took place in laboratories with controlled environments; consequently, the results need to be confirmed outdoors where conditions have greater variability. Analysis adjusting for other confounding factors was not possible due to insufficient data.

3. There is a possibility of publication bias or study selection bias in this meta-analysis. A comprehensive, systematic search was undertaken to limit biased inclusion but the possibility exists that we missed unpublished negative trials. If this were the case, we may be overestimating the effect of NCS treatment. Few authors report numbers of patients excluded from the study prior to randomisation and there is no information on how those excluded differ from those included. We do not know how this would influence the estimate of effect. However, since the effect is very robust considering the diversity of participants and settings, we are reasonably confident of the results.

4. In order to evaluate the effect of baseline severity of EIB on the results, the reviewers selected the mean % fall FEV1 or PEFR in the placebo group for comparison (to adjust for any placebo effect). This was the only outcome to demonstrate a significant difference in effect size. In planning a new primary study, another method for assessing baseline severity or a different cut point may be more appropriate. Stratifying by such a variable may help identify those patients who would most benefit from this drug.

5. Analysis of lung function data was strengthened by the consistency of standardised reporting, which, in the majority of studies, included a measure of variance. Imputing missing standard deviations is a compromise for missing data; however, sensitivity analysis showed no statistically significant differences when comparing results using imputation to only those using recorded values.

6. The small number of studies reporting PEFR results introduces a note of caution, but the concordance with FEV1 results is reassuring.

7. All studies in this review used a crossover design and were assessed as being of good to high quality. The concern regarding inclusion of crossover trails in a meta-analysis are three fold: carry-over effects, period effects, and statistical issues. Data were not reported in a manner that allowed us to confirm the presence or absence of a carryover. However, since EIB is a short, transient condition that returns to baseline values within one hour, and NCS is a short acting agent with rapid clearance from the body and few side effects, we believe the potential for carry-over to be negligible. Were it present, it would bias the treatment effect towards the null and give a more conservative estimate when followed by placebo.

8. Period effect comes into play because EIB is a variable condition and it is possible that baseline PFT values could vary prior to each exercise challenge. Individuals could randomly experience a change in baseline airflow values depending on many of the factors discussed earlier. Had there been a period effect in every study, there would be no reason to believe any systematic bias towards any one period. The large number of studies included, coupled with the variations in ages, sex, country, severity, co-intervention, etc. should ensure an equal distribution of period effects if they exist. By averaging the estimates, the period effect would disappear, leaving an unbiased estimate of the treatment contrast (Senn 1991).

9. No parallel group studies were located in order to compare results from the two methods. Future studies using the crossover method should concentrate on complete reporting of results by period and sequence.

10. Information related to acceptable randomisation, allocation concealment, and blinded outcome assessment was not adequately reported in most of the studies.

11. Finally, data on symptom scores, exercise performance, or subject preference were not included in the studies. Patient assessment of NCS is an important consideration in choosing one treatment over another.

AUTHORS' CONCLUSIONS

Implications for practice

1. A single dose of NCS inhaled 15 to 60 minutes prior to strenuous physical activity is effective in preventing deterioration in lung function during the immediate post-exercise period in adults and children with EIB.

2. The benefit includes a more rapid return to normal lung function.

3. A clear dose-response between 1 mg and 8 mg was not observed; most studies used 4 mg of NCS. There was insufficient data to examine the influence of increasing the dose of NCS according to baseline severity.

4. In these studies, the addition of a spacer device did not influence the treatment effect.

5. There is evidence from subgroup analysis to suggest that NCS provides a greater protective effect in people with more severe EIB.

6. No appreciable adverse effects were demonstrated at a wide range of doses.

Implications for research

Future research should focus on:

1. Correlating physiological benefits with other outcomes such as patient preference, symptom scores, performance effects, costs, etc.

2. Validating the dose response and the duration of response for each dose in both responders and non-responders to NCS.

3. Validating the time course of EIB and return to baseline estimates following treatment.

4. Validating the response in those with more severe EIB in a parallel group study.

5. Comparing NCS to other drugs or in combination with other drugs. Considering the complex physiology involved in EIB, it may not be reasonable to look for a single drug to completely prevent EIB.

6. Conducting a parallel group RCT study that would overcome the methodological limitations of crossover studies and account for confounding introduced by concomitant therapy, climatic conditions, or other issues of interest.

7. Improved reporting of recruitment procedures, methodology and effect estimates accompanied by variance estimates for all outcomes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Boner 1988

Methods	Design: RCT (coding sheet), double-blind, crossover trial. No withdrawals or dropouts. Concomitant Tx: none on steroids in last 3 mos. Stopped SCG & slow release preparations for 1 wk., bronchodilators (BD) for 12 hrs. pre test. Testing: one screening day, 4 test days at same time of day. Exercise test: inclined treadmill, 6 min, heart rate = 86-94% predicted max. for size
Participants	Italy. Recruitment: a residential home for asthmatic children. N=13: 9 m, 4 f. Age: 7.5-13 (mean 10 yrs.) Inclusion: stable asthma, clinical history of EIB (fall FEV1 at least 15%), atopic, proper inhaler technique
Interventions	From randomised code sheet: NCS 4mg or matching placebo via MDI using Auty-Altounyan spacer device or normal adapter 15 min pre-exercise test
Outcomes	Instrument: not reported. Measured: PEFR and FEV1 pre Tx, 5 & 10 min post Tx then at 1, 3, 5, 7, 10 & 15 min. (some 25) post test. Calculated: Max % change FEV1, % protection. Side effects: nothing unusual was reported during the study. Statistics: Anova with patient, Tx and device, area under the curve (fall in function vs. time)
Notes	Jadad score = 4 Author confirmed data extraction within limits, could not access old data. Mean and sd calculated from individual patient data. Time course data: estimated from graph and table.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Boner 1989

Methods	Design: RCT, double-blind, crossover trial. No withdrawals or dropouts. Concomitant Tx: 17 on SCG, 5 on ICS, all on IBD, 2 on OBD. Stopped SCG, ICS, IBD for 24 h. long-acting IBD for 8 h. short-acting IBD for 6 h. pre test. Testing: one screening day, 2 test days. Exercise test: inclined treadmill, 6 min., heart rate = 170-180. T=21-23 C, RH = 50-60%
Participants	Italy. Recruitment: a residential home for asthmatic children. N=20: 15 m, 5 f. Age: 7.5-15 yrs. (mean 11.3)

Boner 1989 (*Continued*)

	Inclusion: asthmatic, atopic, EIB (fall FEV1 at least 15%) mean 39.9%
Interventions	In randomised order in matching inhalers: NCS 4mg or placebo (propellant only) via MDI 30 min. pre-exercise test
Outcomes	Instrument: Vitalograph spirometer. Measured: PEFR, FVC, FEF 25-75, and FEV1 5 min. pre Tx, 5, 10, 20 & 25 min. post Tx, then at 5 min. intervals for 30 min. post test. Mean of pre- test readings used as baseline. Calculated: Max % decrease in lung function as % of pre-test baseline. % protection. Adverse effects: stated ' no unusual symptoms or adverse reactions reported.' Statistics: Anova for repeated measures: Patient's, Tx and Tx order
Notes	Jadad score = 4 Treatment order had little influence on results. Author confirmed data extraction within limits, could not access old data. Time course data estimated from graph. Use pooled sd from other studies.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Bundgaard 1988

Methods	Design: RCT, double- blind, crossover. No withdrawals or dropouts. Concomitant Tx: 5 on theophylline, 9 on ICS, 1 on OCS, 10 on IBD, 1 on chronic oral bronchodilators (OBD) all others had not had steroids in last 3 mos. Stopped theophylline for 24 h. IBD for 12 h. Continued ICS (9pts), 1 on OCS. All given IBD at 30 min. post test or sooner if steady low PEFR reached. Testing: tested at same time of day on consecutive days over 1-2 wks. Exercise test: treadmill, 6 min., T=23C, RH = 45%, Speed adjusted to cause fall in PEFR of 20-50%
Participants	Denmark. Recruitment: (not described) N=14: 6 m, 8 f. Age: 21-49 yrs. (mean=31, sd 7.5). Inclusion: stable asthma, reproducible EIB (fall in PEF > 20%), lung function within 15% predicted normal at time of exercise test. Excluded: if pregnant.
Interventions	Randomised to: NCS 2mg or 4mg or placebo via identical MDI's 30 min. pre test. Monitored technique
Outcomes	Instrument: not reported Measured: PEFR 5 & 10 min. pre Tx, post Tx then 3, 5, 10, 15, 20, & 30 min. post test. (max of 3 readings) Calculated: Max % fall PEFR, mean % fall PEFR at time points. Adverse effects: stated 'no adverse effects reported.' Minor reactions: coughing (2) all Tx, dry throat (1 -

Bundgaard 1988 (*Continued*)

	placebo) itching throat (1 - 4 mg NCS), taste (5 - NCS, 1 - placebo). Reversal IBD tx given within 15 min. to 8 taking placebo, 5 taking NSC 2mg & 2 taking 4mg as part of study protocol. Statistics: Anova for repeated measures
Notes	Jadad score = 4 No author contact to date. Some baseline characteristics outlined in a table.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Chudry 1987

Methods	Design: RCT, double-blind, crossover. Concomitant Tx: stopped SCG, theophylline, IBD 12 hr. pre test. Allowed steroids. Testing: two study days in 1 wk., serial tests on same day: 1 control test, 90 min. later randomized to Tx then tested at 30, 150 and 270 min. post Tx . Exercise test: inclined treadmill, 6 min., HR=170. Ambient room temp
Participants	UK. Recruitment: Asthma clinic. N=12, 9 m, 3 f. Age 8-15 yrs. (mean 13.9) Inclusion: stable Asthma, history of EIB (fall in FEV1 > 20%), good inhalation technique
Interventions	(from pharmacy) In randomised order NCS 4mg or placebo via identical MDI 30 min. pre exercise test
Outcomes	Instrument: rolling seal spirometer. Measured: FEV1 pre and post tx and various times post exercise. Calculated: max % fall FEV1, % protection. Adverse effects: not mentioned Statistics: paired t-test
Notes	Jadad score = 5 There was a significant decline in severity of EIB over course of tests independent of Tx. Author provided confirmation of randomisation and concealment, and provided values and sd not reported in article

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Investigators unaware as to order of randomisation

Comis 1993

Methods	Design: RCT, double-blind, crossover. 7 study days. No withdrawals or dropouts Concomitant Tx: Inhaled medications. Stopped ICS & SCG for 1 wk., IBD 12 h. pre test. Testing: Tests performed at same time daily (each patient completed within 10 days). Exercise test: inclined treadmill, 6 min., Pulse=180, T=22-25 C. RH=35-45%
Participants	Italy. Recruitment: residential school for asthmatics. N=12: 7 m, 5 f. Age: 6.5 - 13.5 yrs. (mean 11) Inclusion: asthmatic, atopic, history of EIB (fall in FEV1 > 15%)
Interventions	Randomised to NCS 4mg, SCG 10mg, or placebo via MDI alone or with a 700ml spacer 30 min. pre test. Placebo = propellant only. Inhalation technique supervised.
Outcomes	Instrument: Vitalograph compact spirometer. Measured: FEV1 before Tx, 30 min after Tx and at end exercise, then 1, 6, 11, 16, 21, 26, 30 min. post test. Calculated: max % fall in FEV1, % protection. Adverse effects: not reported Statistics: Anova for repeated measures, paired t-test.
Notes	Jadad score = 3 Author confirmed data extraction within limits, could not access old data

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

De Benedictis 1994a

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: theophylline, IBD, SCG, NCS, ICS. No OCS. Stopped theophylline for 24 h., other drugs for 12 h. before each test. Testing: Screening plus 3 tests at same time on separate days, completed within 10 days. Exercise test: inclined treadmill, 6 min., pulse=85% of max predicted for age. T=21-23C, RH 48-58%
Participants	Italy. Recruitment: pediatric asthma clinic. N=17: 11 m, 6 f. Age: 7-15 yrs (mean 10.2 +/- 2.2 yr.) Inclusion: asthma, reproducible EIB (fall in FEV1 at least 15%) Baseline FEV1 > 70% predicted normal and varied < 10% from previous study day. No RI in previous 4 wks
Interventions	Random, blinded order: NCS 4 mg or SCG 10 mg or placebo via MDI (2 used a spacer) using closed lip technique 20 min. pre exercise test

De Benedictis 1994a (*Continued*)

Outcomes	Instrument: turbine spirometer, & Knudson's predicted values. Measured: FEV1 pre Tx, pre-exercise then 3, 5, 10, 15, 30 min. post exercise. Pulse monitored pre/post exercise. Calculated: Max % fall in FEV1, % protection. Adverse effects: not reported. Statistics: Anova for repeated measures, paired t-test.
Notes	Jadad score = 3 Author contacted and confirmed data extraction. Time course values estimated from graph.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

De Benedictis 1994b

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: theophylline, IBD, SCG, NCS, ICS. No OCS. Stopped theophylline for 24 h., other drugs for 12 h. before each test. Testing: Screening plus 3 test days at same time on separate days, completed within 10 days. Exercise test: inclined treadmill, 6 min., pulse=85% of max predicted for age. T=21-23C, RH 48-58%
Participants	Italy. Recruitment: pediatric asthma clinic. N=8 children, 5 m, 3 f. Age: 7-11 yrs. (mean 8.7) Inclusion: asthmatic, reproducible EIB (fall in FEV1 at least 15%), baseline FEV1 > 70% predicted normal and varied < 10% from previous study day. No RI in previous 4 wks
Interventions	Randomised to: NCS 4mg or SCG 10mg or placebo via MDI with Aerochamber spacer 20 min. pre exercise test. Inhalation technique monitored
Outcomes	Instrument: turbine spirometer & Knudson's predicted values. Measured: FEV1 pre Tx, pre-exercise then 3, 5, 10, 15, 30 min. post exercise. Pulse monitored pre/post exercise but not reported Calculated: Max % fall in FEV1, % protection Adverse effects: not reported. Statistics: Anova for repeated measures, paired t-test,
Notes	Jadad score = 3 Author confirmed mean % fall NCS=14.8, sd 18.6. Author contacted and confirmed data extraction.

Risk of bias

De Benedictis 1994b (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

De Benedictis 1995

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: theophylline, IBD, SCG, NCS, ICS. No OCS. Stopped theophylline for 24 h., other drugs for 12 h. before each test. None on oral steroids. Testing: screening plus 3 test days at same time on separate days, completed within 10 days. Exercise test: inclined treadmill, 6 min., pulse=85% of max predicted for age. T=21-23C, RH 48-58%
Participants	Italy. Recruitment: pediatric asthma clinic. N=13: 9 m, 4 f. Age: 7-15 yrs. (mean 10, sd 2.3) Inclusion: asthmatic, reproducible EIB (fall in FEV1 at least 15%), baseline FEV1 > 70% predicted normal and varied < 10% from previous study day. No RI in previous 4 wks
Interventions	Random, blind order: NCS 4mg or SCG 10mg or placebo via MDI using closed lip technique 20 min. & 140 min. pre exercise test. Technique monitored
Outcomes	Instrument: turbine spirometer & Knudson's predicted values Measured: FEV1 pre Tx, pre-exercise then 3, 5, 10, 15, 30 min. post exercise. Pulse monitored pre/post exercise. Calculated: Max % fall in FEV1, % protection. Adverse effects: not reported. Statistics: Anova, Wilcoxin signed-rank test
Notes	Jadad score = 3 Author stated that subjects in these three studies were discrete individuals

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Debelic 1986

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: not mentioned. Testing: screening plus 2 test days at same time on separate days, completed within 5 days. Exercise test: free running in corridor at room temp.

Debelic 1986 (*Continued*)

Participants	Germany. Recruitment: not described. N=12: 7 m, 5 f. Age: 14-19 yrs. (mean 16.9) Inclusion: atopic, bronchial hyperreactivity, reproducible EIB (fall in FEV1 > 20%) Baseline FEV1> 70% normal values
Interventions	Randomised to: NCS 4mg vs placebo via MDI 30 min. pre exercise test
Outcomes	Instrument: not reported Measured: FEV1 pre Tx, 10 & 20 min. post Tx, then 1, 3, 5, 10 min. post exercise. Calculated: Max % fall FEV1, % protection. Adverse effects: stated 'no side effects observed'. Statistics: Anova with patients, Tx
Notes	Jadad score = 3 Time course data calculated from graphs. Max % fall FEV1 and sd provided by author. Author contacted and provided raw data.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Henriksen 1988

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: all on IBD, 4 on SCG, 2 on theophylline, 2 on OBD, 1 on ICS. Stopped oral anti-asthma drugs & SCG for 24 h., IBD for 12 h. before each test, ICS continued. Testing: control plus 2 test days no more than 1 wk. apart. Exercise test: treadmill, 5-6 min., HR =180. Work load 2.8-3.4 watts/kg body wt. Used a nose clip. T & RH measured
Participants	Denmark. Recruitment: not described. N=12, 10 m, 2 f. Age: 7-14 yrs. (mean 10.8) Inclusion: atopic, had perennial episodes of airway obstruction, history of EIB (fall in FEV1 at least 20%) baseline PEFR or FEV1 not less than 70% predicted normals
Interventions	Randomised to: NCS 4mg or placebo via identical MDI's 30 min. pre exercise test
Outcomes	Instrument: Wright's PEF meter and electronic spirometer. Measured: FEV1 & PEFR, best of 3 readings, pre & post Tx, 10 & 5 min. pre exercise, then at 2, 5, 10, 20, 30 min. post exercise or until maximum fall recorded. All terminated with IBD at 30 min. or earlier if required. Calculated: Max % fall PEF or FEV1, % protection, effect of treatment order, effect on heart rate. Adverse effects: stated 'no unusual symptoms or adverse reactions were reported'. Statistics: Anova using patient, Tx, Tx order

Henriksen 1988 (*Continued*)

Notes	Jadad score = 4 Tx order had no effect on result. Small but significant increase in heart rate with NCS treatment over control run. sd for mean max % fall FEV1 imputed from pooled results of other studies. sd for mean max % fall PEFR calculated from individual patient data in article. No author contact to date.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Konig 1987

Methods	Design: RCT, double-dummy, crossover. No withdrawals or dropouts. Concomitant Tx: theophylline, IBD. Stopped theophylline for 48 h., IBD for 12 h. before each test. Testing: control plus 3 test days at same time of day, completed in 10 days. Participant performed 3 exercise tests on each study day. Exercise test: inclined treadmill, 6 min., HR=90% max predicted for age. T=21.3-21.5, RH=48 - 50.4 %
Participants	USA. Recruitment: not described. N=12 m. Age: 21-38 yrs. (mean 27.3) Inclusion: asthmatic, reproducible EIB (fall in FEV1 at least 20%), baseline FEV1 > 70% normal, no URI's in last 3 wks. Excluded: if on SCG or oral steroids in last month. FEV1 varied <15% between test days
Interventions	In random order: 1) NCS 4mg MDI plus placebo spinhaler capsule. 2) placebo MDI plus SCG 20 mg spinhaler capsule or 3) placebo MDI plus placebo spinhaler capsule 20 min. pre exercise test. Technique monitored. Test repeated at 2 & 4 hrs. post Tx
Outcomes	Instrument: wedge spirometer & Knudson predicted values. Measured: FEV1, FVC, FEF 25-75. pre Tx, 20 min. post Tx, then 3, 5, 10, 15, 20, 30 min. post exercise. Exercise test repeated without additional medication at 120 & 240 min. post Tx. Calculated: Max % fall FEV1, % protection. Adverse effects: none Statistics: Anova
Notes	Jadad score = 3 Repeated challenges at 2 hr. intervals did not affect degree of EIB. No author contact to date.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Mihalyka 1988

Methods	Design: RCT, double blind, crossover. No withdrawals or dropouts. Concomitant Tx: stopped IBD, SCG IB for 5 h., oral medications for 12 h. pre test. Exercise test: treadmill running, 8 min., room air
Participants	Australia. Recruitment: not described. N=14 (sex not reported). Age: 15 - 45 yrs. Inclusion: stable asthma, history of EIB (fall in PEFR at least 20%)
Interventions	Randomised to: NCS 4mg or placebo via MDI 15 min. pre-exercise
Outcomes	Instrument: Minato Spirometer. Measured: max % fall PEFR pre exercise, post exercise. Calculated: max % fall PEFR. Pulse recorded. Adverse effects: bad taste (4 NCS)
Notes	Jadad score =3 No significant difference in heart rate. Author provided some unpublished individual patient data.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Information not available

Morton 1992

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: SCG, IBD, ICS. Stopped IBD for 4h., long-acting BD for 12h., SCG, theophyllines, & H1 antagonists for 24 h. pre test. Continued on inhaled steroids if had been on them at least 4 wks. 3 excluded because fall in FEV1 < 15% with all Tx. Testing: screening plus 4 study days at same time of day, completed in 11 days. Exercise test: inclined treadmill, 8 min. at 70% VO2 max. T=20 +/- 2 C, RH=40 - 54%. No food or fluid 2 h. pre-test, allowed 1 cup of caffeinated fluid or 1 chocolate bar on test day, avoided vigorous exercise for 24 h. and total abstinence from exercise for 4 h. pre-test. Exercise test: inclined treadmill, 8 min, VO2 ~ 70% max
Participants	Australia. Recruitment: not described N=16, 10 m, 6 f. Age: 13-30 yrs. (mean 20, sd 4.84) Inclusion: asthmatic, non-smokers, history of EIB (at least a 15% fall in FEV1) FEV1 > 75% personal best. (2 m & 1 f excluded on this basis) 16 analysed. Excluded: if on OCS in last 4 wks.
Interventions	Random assignment to NCS 8mg, SCG 4mg, placebo (propellant gas & sorbitan trioleate) or no TX via identical MDI's 15 min. pre-exercise test. Technique monitored

Morton 1992 (*Continued*)

Outcomes	Instrument: single wedge dry spirometer (highest of 2 trials). Measured: FEV1 pre-Tx, pre-exercise and immediately then 5, 10, 15, 20, 25 & 30 min. post exercise. Calculated: max % fall FEV1, % protection. Adverse effects: unpleasant taste (12 NCS, 1 placebo), throat irritation (3 NCS). Statistics: Anova.
Notes	Jadad score = 4 Author contacted but no additional data provided.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Novembre 1994f

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: all on IBD, 6 on SCG or NCS, 2 on ICS, 4 on theophylline. Stopped oral BD & long acting BD for 12 h., short acting BD for 6 h. Exclusions: those on SCG or inhaled steroids in past month. Testing: screening plus 4 test days at same time of day, every other day, completed over 3 wks. in Jan. - Feb. Exercise test: inclined treadmill, 6 min, HR=170-180, T=20-22 C, RH=45-50%
Participants	Italy. Recruitment: not described. N=24. 16 m, 8 f. Age: 6-16 yrs. Inclusion: asthmatic, atopic, no URI in past 3 wks. History of EIB (fall in FEV1at least 15%) Excluded: those on SCG or ICS in past month.
Interventions	In random order: 1) NCS 4 mg via MDI with large vol. spacer plus placebo (NS) x 15 min. via jet nebulizer. 2) Placebo (propellant only) MDI plus furosemide 30 mg neb. 3) NCS via MDI plus furosemide neb. 4) Placebo MDI plus placebo neb
Outcomes	Instrument: pneumotachograph, predicted values from Zapletal et al. Measured: FEV1, PEFR, FEF15-75 pre-Tx, pre-exercise test then 2, 4, 6, 8, 10, 15, 20, 30 min. post exercise. Calculated: max % fall FEV1, PEFR and FEF25-75, % fall FEV1 at different time points, % protection. Adverse effects: unpleasant taste (6 NCS), mild throat irritation (3NCS), headache (1 placebo), Statistics: Anova
Notes	Jadad score = 3 'Treatment order had little influence on results'. No author contact to date.

Risk of bias

Item	Authors' judgement	Description

Novembre 1994f (*Continued*)

Allocation concealment?	Unclear	Information not available

Novembre 1994s

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: All on IBD, 6 on SCG, 3 on theophylline, 2 on ICS. Stopped BD & long acting BD's for 12 h., short acting BD's for 6 h. Testing: screening plus 3 test days at same time of day, separate days. Exercise test:iInclined treadmill, 6 min., HR=170-180, T=20-22 C, RH=45-50%
Participants	Italy. Recruitment: not described. N=19. 13 m, 6 f. Age: 6-15 yrs. Inclusion: asthmatic, atopic, history of EIB (Fall in FEV1 at least 15 %), no URI in past 3 wks, FEV1 > 92% predicted normal at time of testing. Exclusions: SCG or inhaled steroids in past month.
Interventions	In random order: NCS 4mg or SCG 10mg or placebo via MDI plus large volume spacer 20 min pre-exercise test. Technique monitored
Outcomes	Instrument: pneumotachograph. Measured: FEV1, PEFR, FEF15-75 pre-Tx, pre-exercise test then 1, 5, 10, 15, 20 min post exercise. Calculated: max % fall FEV1, PEFR and FEF25-75, mean % fall FEV1 at time points, % protection. Adverse effects: unpleasant taste (4 NCS, 2 SCG). Statistics. T-test
Notes	Jadad score = 3 No author contact to date. Time course data from table with sd reported.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Information not available

Oseid 1995

Methods	Design: RCT, double-blind, crossover. One withdrawal post placebo due to worsening asthma. (did not do NCS Tx and not analysed). Concomitant Tx: IBD, 2 on ipratropium bromide, 7 on SCG, 1 on theophylline. Stopped: Astemizole for 3 wks, SCG or antihistamines for 3 days, OBD and ipratropium for 12 h., IBD for 8 h. pre-test. Sustained release BD changed to short-term oral BD 1 wk. pre-test. Testing: 2 screen days, 2 study days, at same time of day on consecutive days. Exercise test: bicycle ergometer, 8 min. Work effort monitored (70% VO2 max). T= -18+-5 C, dry air
Participants	Norway. Recruitment: clinic. N=20. 6m, 14 f. Age: 15-28 yrs. (mean 18.9 +-3.73)

Oseid 1995 (*Continued*)

	Inclusion: stable asthma, atopic, non-smokers, history of EIB exacerbated by cold air, (fall FEV1 > 20%) current FEV1 > 75% predicted, mild to moderate BHR (PC20 methacholine <8.0 mg/ml). Excluded: pregnancy, nocturnal asthma, clinically relevant diseases, no OCS or ICS in past 3 mo
Interventions	In random order: NCS 4mg or placebo via identical MDI's 30 min. pre-exercise test. Placebo = sorbitan trioleate surfactant & chlorofluorocarbon propellant). Technique monitored
Outcomes	Instrument: not reported Measured: FEV1, FVC, FEF25-75. pre tx then 5 & 29 min. post TX then 0, 3, 6, 10, 15, 20 min. post exercise. Calculated: Max % fall FEV1, % change at each time point. Adverse effects: migrane headache (1 placebo). Statistics: stratified Anova with Tx, period, sequence as factors, paired t-tests
Notes	Jadad score = 4 No author contact to date.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Roberts 1985

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: 10 on SCG, 14 on IBD, 1 on IB, 3 on ICS. Stopped SCG for 24 h. & IBD's for 12 h. pre-test. Continued on ICS. None on oral steroids. Testing: control plus 3 test days, same time of day, separate days. Exercise test: inclined treadmill, 5-8 min, P=170, T=20-22 C, RH=40 - 60 %
Participants	Glasgow, UK. Recruitment: not described. N=9 (6 m, 3 f) Age: 16-50 yrs. (mean 31.1) Inclusion: asthmatic, atopic, history of EIB (fall in FEV1 at least 20%)
Interventions	Randomised to: NCS 2 mg or 4 mg or placebo via identical MDI 30 min. pre-exercise test
Outcomes	Instrument: dry spirometer. Measured: FEV1, Pre Tx, 25 min. post Tx then 2, 5, 10, 15, 20, 30 min. post exercise. Calculated: % fall FEV1. Adverse effects: none complained of. Statistics: Paired t-test, Anova
Notes	Jadad score = 4 No author contact to date.

Risk of bias

Roberts 1985 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Shaw 1985

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: inhaled medications only. Stopped ICS, SCG for one wk., IBD for 8 h. pre test. Testing: control plus 2 study days 1 wk. apart. Exercise test: inclined treadmill, 6-12 min., until FEV1 decreased by > 15%. Ambient room temp and humidity
Participants	UK. Recruitment: not described. N=8 m. Age: 17-47 yrs. Inclusion: asthma, non-smokers, atopic, history of EIB (fall in FEV1 at least 15%), pre test FEV1 ranged from 45-115% predicted (mean 86%)
Interventions	Random order: NCS 2mg or placebo via identical MDI's 20 min. pre-exercise
Outcomes	Instrument: Vitalograph. Measured: FEV1, FVC pre Tx, pre-exercise then 2, 5, 10, 15, 20, & 25 min. post exercise. Calculated: mean % fall FEV1 at time points Adverse effects: none experienced. Statistics: Wilcoxin matched pairs signed ranks test.
Notes	Jadad score = 4 Use individual patient data to calculate mean max % fall FEV1 and sd. Author contacted, could not access data.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Sinclair 1990

Methods	Design: RCT, (coded in pharmacy) double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: not described. Stopped BD's for 24 h. pre test. Testing: Tests on 3 consecutive days between 9:30 - 11:30 AM Exercise test: inclined treadmill, 6 min, T 17-25 C
Participants	UK. Recruitment: not described. N=20. 18 m, 2 f. Age: 17-28 yrs., (mean 20.7) Inclusion: reproducible EIB (fall % FEV1 at least 15%)

Sinclair 1990 (*Continued*)

	Exclusion: those on OCS, ICS, NCS or SCG.
Interventions	Randomised to: NCS 4mg, SCG 10mg or placebo via coded MDI's 30 min. pre exercise
Outcomes	Instrument: Vitalograph. Measured: FEV1 pre exercise then 1, 3, 5, 7, 9 min. post exercise. Calculated: mean % fall FEV1 at time points. Statistics: Anova
Notes	Jadad score = 5 Author contacted. Unable to provide further information.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Investigators unaware as to order of randomisation

Thomson 1986

Methods	see Roberts 1985
Participants	see Roberts 1985
Interventions	see Roberts 1985
Outcomes	see Roberts 1985
Notes	see Roberts 1985

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Todaro 1993

Methods	Design: RCT, double-blind, crossover. No withdrawals or dropouts. Concomitant Tx: none on chronic Tx. Stopped SCG, IBD for 24 h. pre test. Testing: Control plus tests on separate days. Exercise test: based on the type of sport practiced. Work effort monitored. T=19-25 C. RH=45-52%
Participants	Italy. Recruitment: high level athletes - 7 on Olympic team. N=13. 11 m, 2f. Age: 19-31 yrs. (mean 25). Inclusion: well documented EIB (fall FEV1 >10%, all 13 were > 15%), FEV1/FVC range 60.3 - 87.8 (mean 70.2, sd 8.0)

Todaro 1993 (*Continued*)

Interventions	In random order to: NCS 4mg or placebo via MDI 20 min. pre exercise test
Outcomes	Used: turbine spirometer Measured: FEV1 pre Tx, pre-exercise then immediately and 5, 10, 15, 20, 30 min. post exercise. HR monitored. Calculated: max % fall FEV1, mean fall % FEV1 at time points, % protection. Adverse effects: bronchospasm (1 NCS). Beneficial effects: recovery values above baseline. Anova, paired t-test.
Notes	Jadad score = 3 No significant difference in heart rate. Author contacted, no additional data provided.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available

Vilsvik 1988

Methods	Design: RCT, (Latin square) double-blind, crossover. 9 excluded because did not show a reproducible fall of 20%, 2 excluded because > 15% variation from control day. Concomitant Tx: none on OBD or theophylline. Stopped IBD 8 h. pre test. Testing: 2 control, 4 study days at same time in AM on different days (1-7 days apart). Exercise test: inclined treadmill, 6 min., T=22 C, RH=55%. HR monitored
Participants	Norway. Recruitment: not described. N=12. 9 m, 3, f. Age: 20-45 yrs. (mean 29) Inclusion: asthma, reproducible EIB (fall FEV1 at least 20% in 2 control tests 1 wk apart), FEV1 > 70% predicted, < 15% variability over study period. Exclusions: 9 of 23 excluded because failed to demonstrate reproducible EIB, 2 of 23 showed > 15% variability. 12 subjects analysed
Interventions	Randomised to: NCS 1mg, 4mg, 8mg or placebo via identical MDI's 60 min. pre exercise. Plasma concentrations monitored
Outcomes	Instrument: not reported Measured: PEFR pre/post Tx, pre-exercise, then 2, 5, 10, 15, and 30 min. post exercise. Calculated: Maximum % fall PEFR, % protection, Adverse effects: 9 required IBD rescue 16 times (8 placebo, 8 NCS). 4 patients, 2 complaints: taste, irritated throat Statistics: repeated measures Anova
Notes	Jadad score = 4 No differences in heart rate. sd calculated from individual patient data provided.

Vilsvik 1988 (*Continued*)

	Author contacted, no additional data provided.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Investigators unaware as to randomisation sequence.

Individual data provided.
This study excluded. It only included known responders to NCS.

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

Study	Reason for exclusion
Albazzaz 1989	Patients selected on the basis they were known responders to nedocromil sodium
Albazzaz 1992	Patients selected on the basis they were known responders to nedocromil sodium
Bauer 1986	Not the required outcome measures included
Bauer 1988	Not the required outcome measures included.
Bleeker 1995	Abstract only. Control was an active drug.
Cavallo 1995	Not an RCT.
de Benedictis 1998	Examined the effect of nedocromil/salbutamol in a single formulation vs. salbutamol vs. placebo
Hoffmeister 1995	The control used was an active drug.
Magnussen 1986	Communication from author: not an RCT. Original study published in German and was not translated based on author's comments
Patel 1987	Abstract only. Author contacted - full text not available.
Speelberg 1992	Participants were mix of asthma and COPD. Not all had an early EIB response. Late reaction EIB not studied in this analysis
Valero A 1996	Open label trial. No placebo group.

DATA AND ANALYSES

Comparison 1. NCS vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum % fall FEV1	17	480	Mean Difference (IV, Random, 95% CI)	-15.64 [-18.14, -13.15]
1.1 Children	11	324	Mean Difference (IV, Random, 95% CI)	-14.81 [-18.16, -11.45]
1.2 Adults	6	156	Mean Difference (IV, Random, 95% CI)	-16.89 [-20.81, -12.97]
2 Maximum % fall PEFR	7	230	Mean Difference (IV, Random, 95% CI)	-14.98 [-21.62, -8.34]
2.1 Children	4	150	Mean Difference (IV, Random, 95% CI)	-11.48 [-18.48, -4.49]
2.2 Adults	3	80	Mean Difference (IV, Random, 95% CI)	-19.25 [-30.85, -7.65]
3 Maximum fall % FVC	3	96	Mean Difference (IV, Random, 95% CI)	-7.00 [-16.32, -1.67]
4 Maximum fall % FEF25-75	5	190	Mean Difference (IV, Random, 95% CI)	-16.47 [-22.88, -10.05]

Comparison 2. Dose NCS vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum fall FEV1	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 2 mg or less MDI	2	34	Mean Difference (IV, Random, 95% CI)	-24.37 [-32.20, -16.54]
1.2 4 mg MDI	15	432	Mean Difference (IV, Random, 95% CI)	-14.51 [-16.98, -12.04]
1.3 > 4 mg MDI	1	32	Mean Difference (IV, Random, 95% CI)	-22.53 [-33.54, -11.52]
2 Maximum fall PEFR	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 2 mg or less MDI	2	52	Mean Difference (IV, Random, 95% CI)	-13.36 [-21.27, -5.46]
2.2 4 mg MDI	7	230	Mean Difference (IV, Random, 95% CI)	-14.98 [-21.62, -8.34]
2.3 > 4 mg MDI	1	24	Mean Difference (IV, Random, 95% CI)	-21.80 [-34.59, -9.01]

Comparison 3. Different delivery system NCS vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum % fall FEV1	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 4 mg areosolized NCS using spacer	5	152	Mean Difference (IV, Random, 95% CI)	-13.89 [-18.02, -9.76]
1.2 4 mg areosolized NCS regular adapter	12	330	Mean Difference (IV, Random, 95% CI)	-14.75 [-17.71, -11.79]
2 Maximum % fall PEFR	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 4 mg areosolized NCS using spacer	2	86	Mean Difference (IV, Random, 95% CI)	-8.50 [-13.95, -3.05]
2.2 4 mg areosolized NCS regular adapter	5	144	Mean Difference (IV, Random, 95% CI)	-18.02 [-27.07, -8.97]

Comparison 4. Duration of action NCS vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum fall FEV1	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 120 - 150 min post treatment	3	74	Mean Difference (IV, Random, 95% CI)	-5.95 [-12.89, 0.99]
1.2 240 - 270 min post treatment	2	48	Mean Difference (IV, Random, 95% CI)	-5.66 [-14.17, 2.84]

Comparison 5. Severity of EIB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum % fall FEV1	17	480	Mean Difference (IV, Random, 95% CI)	-15.64 [-18.14, -13.15]
1.1 Mild EIB (< 30% maximum fall FEV1)	9	302	Mean Difference (IV, Random, 95% CI)	-12.84 [-15.65, -10.03]
1.2 Moderate-Severe EIB (30% or greater maximum fall in FEV1)	8	178	Mean Difference (IV, Random, 95% CI)	-21.36 [-25.52, -17.20]
2 Maximum % fall PEFR	7	230	Mean Difference (IV, Random, 95% CI)	-14.98 [-21.62, -8.34]
2.1 Mild EIB (< 30% maximum fall PEFR)	4	154	Mean Difference (IV, Random, 95% CI)	-8.30 [-12.49, -4.10]

2.2 Moderate-Severe EIB (30% or greater maximum fall in PEFR)	3	76	Mean Difference (IV, Random, 95% CI)	-25.14 [-31.61, -18.67]

Comparison 6. Effect of time of pretreatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 maximum % fall FEV1	17	480	Mean Difference (IV, Random, 95% CI)	-15.66 [-18.15, -13.17]
1.1 < 30 minutes pre-exercise	10	286	Mean Difference (IV, Random, 95% CI)	-15.05 [-17.87, -12.22]
1.2 30 minutes or more pre-exercise	7	194	Mean Difference (IV, Random, 95% CI)	-17.03 [-22.26, -11.80]
2 maximum % fall PEFR	7	230	Mean Difference (IV, Random, 95% CI)	-14.98 [-21.62, -8.34]
2.1 < 30 minutes minutes pre-exercise	3	114	Mean Difference (IV, Random, 95% CI)	-8.55 [-13.35, -3.74]
2.2 30 minutes or more pre-exercise	4	116	Mean Difference (IV, Random, 95% CI)	-20.47 [-31.03, -9.91]

Comparison 7. NCS inclusive vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 mean maximum % fall FEV1	17	480	Mean Difference (IV, Random, 95% CI)	-15.64 [-18.14, -13.15]
2 mean maximum % fall PEFR	7	230	Mean Difference (IV, Random, 95% CI)	-14.98 [-21.62, -8.34]

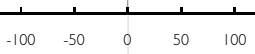
Analysis 1.1. Comparison 1 NCS vs placebo, Outcome 1 Maximum % fall FEV1.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 1 NCS vs placebo

Outcome: 1 Maximum % fall FEV1

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Children							
Boner 1988	13	13.54 (13.85)	13	20.77 (21.46)		3.1 %	-7.23 [-21.11, 6.65]
Novembre 1994f	24	15.42 (8.35)	24	28.46 (13.84)		12.1 %	-13.04 [-19.51, -6.57]
De Benedictis 1994b	8	14.8 (18.6)	8	31.4 (20.6)		1.6 %	-16.60 [-35.83, 2.63]
Novembre 1994s	19	11 (12.4)	19	26.1 (14.9)		7.3 %	-15.10 [-23.82, -6.38]
De Benedictis 1994a	17	14.4 (11.1)	17	27.4 (17.3)		5.9 %	-13.00 [-22.77, -3.23]
De Benedictis 1995	13	15.7 (16.8)	13	29.6 (18.9)		3.1 %	-13.90 [-27.65, -0.15]
Boner 1989	20	15.7 (13.1)	20	22.7 (16.47)		6.6 %	-7.00 [-16.22, 2.22]
Henriksen 1988	12	17.5 (13.1)	12	47.2 (16.47)		4.1 %	-29.70 [-41.61, -17.79]
Chudry 1987	12	21.3 (13.1)	12	39.7 (12.9)		5.3 %	-18.40 [-28.80, -8.00]
Comis 1993	12	14.5 (12.2)	12	31.3 (15.1)		4.8 %	-16.80 [-27.78, -5.82]
Debelic 1986	12	29.83 (15.95)	12	48.08 (15.08)		3.8 %	-18.25 [-30.67, -5.83]
Subtotal (95% CI)	**162**		**162**			**57.8 %**	**-14.81 [-18.16, -11.45]**
Heterogeneity: Tau² = 3.59; Chi² = 11.25, df = 10 (P = 0.34); I² =11%							
Test for overall effect: Z = 8.65 (P < 0.00001)							
2 Adults							
Morton 1992	16	15.83 (13.43)	16	38.36 (18.01)		4.8 %	-22.53 [-33.54, -11.52]
Shaw 1985	8	10.27 (7.02)	8	34.43 (10.96)		6.9 %	-24.16 [-33.18, -15.14]
Konig 1987	12	12 (14.6)	12	26.2 (12.3)		4.9 %	-14.20 [-25.00, -3.40]
Todaro 1993	13	10.1 (8.9)	13	23.5 (4)		16.6 %	-13.40 [-18.70, -8.10]
Roberts 1985	9	18.9 (17.7)	9	38.9 (18.9)		2.1 %	-20.00 [-36.92, -3.08]
Oseid 1995	20	14.1 (9.5)	20	28.9 (18)		7.0 %	-14.80 [-23.72, -5.88]
Subtotal (95% CI)	**78**		**78**			**42.2 %**	**-16.89 [-20.81, -12.97]**
Heterogeneity: Tau² = 3.13; Chi² = 5.71, df = 5 (P = 0.34); I² =12%							
Test for overall effect: Z = 8.45 (P < 0.00001)							
Total (95% CI)	**240**		**240**			**100.0 %**	**-15.64 [-18.14, -13.15]**
Heterogeneity: Tau² = 2.44; Chi² = 17.57, df = 16 (P = 0.35); I² =9%							
Test for overall effect: Z = 12.30 (P < 0.00001)							



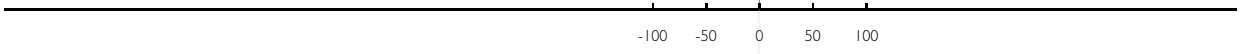
Analysis 1.2. Comparison 1 NCS vs placebo, Outcome 2 Maximum % fall PEFR.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 1 NCS vs placebo

Outcome: 2 Maximum % fall PEFR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Children							
Boner 1989	20	10 (11.03)	20	17.5 (16.19)		15.4 %	-7.50 [-16.09, 1.09]
Novembre 1994s	19	9.1 (10.9)	19	19.5 (16.9)		15.0 %	-10.40 [-19.44, -1.36]
Novembre 1994f	24	15.04 (7.9)	24	22.46 (15.13)		17.0 %	-7.42 [-14.25, -0.59]
Henriksen 1988	12	17.81 (14.21)	12	45.2 (19.66)		11.0 %	-27.39 [-41.11, -13.67]
Subtotal (95% CI)	**75**		**75**			**58.5 %**	**-11.48 [-18.48, -4.49]**
Heterogeneity: Tau² = 28.52; Chi² = 7.04, df = 3 (P = 0.07); I² =57%							
Test for overall effect: Z = 3.22 (P = 0.0013)							
2 Adults							
Bundgaard 1988	14	21.3 (11.03)	14	41.3 (16.19)		13.9 %	-20.00 [-30.26, -9.74]
Vilsvik 1988	12	15 (11.96)	12	44.2 (14.18)		13.7 %	-29.20 [-39.70, -18.70]
Mihalyka 1988	14	13.2 (12)	14	21.9 (15.3)		14.0 %	-8.70 [-18.89, 1.49]
Subtotal (95% CI)	**40**		**40**			**41.5 %**	**-19.25 [-30.85, -7.65]**
Heterogeneity: Tau² = 77.42; Chi² = 7.59, df = 2 (P = 0.02); I² =74%							
Test for overall effect: Z = 3.25 (P = 0.0011)							
Total (95% CI)	**115**		**115**			**100.0 %**	**-14.98 [-21.62, -8.34]**
Heterogeneity: Tau² = 55.24; Chi² = 20.28, df = 6 (P = 0.002); I² =70%							
Test for overall effect: Z = 4.42 (P < 0.00001)							



Analysis 1.3. Comparison 1 NCS vs placebo, Outcome 3 Maximum fall % FVC.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

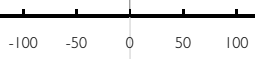
Comparison: 1 NCS vs placebo

Outcome: 3 Maximum fall % FVC

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Boner 1989	20	10.6 (9.2)	20	14.7 (9.2)		39.9 %	-4.10 [-9.80, 1.60]
Oseid 1995	20	10.3 (7.8)	20	17.9 (12.8)		36.9 %	-7.60 [-14.17, -1.03]
Shaw 1985	8	4.24 (4.73)	8	23.88 (15.71)		23.2 %	-19.64 [-31.01, -8.27]
Total (95% CI)	**48**		**48**			**100.0 %**	**-9.00 [-16.32, -1.67]**

Heterogeneity: Tau^2 = 26.58; Chi^2 = 5.74, df = 2 (P = 0.06); I^2 =65%

Test for overall effect: Z = 2.41 (P = 0.016)



Analysis 1.4. Comparison 1 NCS vs placebo, Outcome 4 Maximum fall % FEF25-75.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

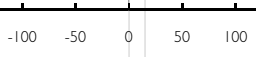
Comparison: 1 NCS vs placebo

Outcome: 4 Maximum fall % FEF25-75

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Boner 1989	20	37.8 (20)	20	48 (20)		26.8 %	-10.20 [-22.60, 2.20]
Konig 1987	12	21.8 (23.2)	12	40.4 (16.3)		16.0 %	-18.60 [-34.64, -2.56]
Novembre 1994f	24	36.29 (27.33)	24	60.21 (33.09)		14.0 %	-23.92 [-41.09, -6.75]
Novembre 1994s	19	22 (25.4)	19	37.7 (21.8)		18.2 %	-15.70 [-30.75, -0.65]
Oseid 1995	20	24 (18.7)	20	42.2 (22.4)		25.1 %	-18.20 [-30.99, -5.41]
Total (95% CI)	**95**		**95**			**100.0 %**	**-16.47 [-22.88, -10.05]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.85, df = 4 (P = 0.76); I^2 =0.0%

Test for overall effect: Z = 5.03 (P < 0.00001)



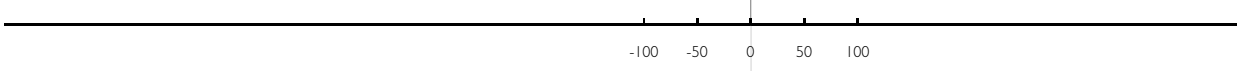
Analysis 2.1. Comparison 2 Dose NCS vs placebo, Outcome 1 Maximum fall FEV1.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 2 Dose NCS vs placebo

Outcome: 1 Maximum fall FEV1

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 2 mg or less MDI							
Roberts 1985	9	13.9 (15)	9	38.9 (18.9)		26.3 %	-25.00 [-40.76, -9.24]
Shaw 1985	8	10.27 (7.02)	8	34.43 (10.96)		73.7 %	-24.16 [-33.18, -15.14]
Subtotal (95% CI)	**17**		**17**			**100.0 %**	**-24.37 [-32.20, -16.54]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$							
Test for overall effect: Z = 6.10 (P < 0.00001)							
2 4 mg MDI							
Boner 1988	13	13.54 (13.85)	13	20.77 (21.46)		3.5 %	-7.23 [-21.11, 6.65]
Boner 1989	20	15.7 (13.1)	20	22.7 (16.47)		7.5 %	-7.00 [-16.22, 2.22]
Chudry 1987	12	21.3 (13.1)	12	39.7 (12.9)		6.0 %	-18.40 [-28.80, -8.00]
Comis 1993	12	14.5 (12.2)	12	31.3 (15.1)		5.5 %	-16.80 [-27.78, -5.82]
De Benedictis 1994a	17	14.4 (11.1)	17	27.4 (17.3)		6.8 %	-13.00 [-22.77, -3.23]
De Benedictis 1994b	8	14.8 (18.6)	8	31.4 (20.6)		1.9 %	-16.60 [-35.83, 2.63]
De Benedictis 1995	13	15.7 (16.8)	13	29.6 (18.9)		3.6 %	-13.90 [-27.65, -0.15]
Debelic 1986	12	29.83 (15.95)	12	48.08 (15.08)		4.4 %	-18.25 [-30.67, -5.83]
Henriksen 1988	12	17.5 (13.1)	12	47.2 (16.47)		4.7 %	-29.70 [-41.61, -17.79]
Konig 1987	12	12 (14.6)	12	26.2 (12.3)		5.6 %	-14.20 [-25.00, -3.40]
Novembre 1994f	24	15.42 (8.35)	24	28.46 (13.84)		13.6 %	-13.04 [-19.51, -6.57]
Novembre 1994s	19	11 (12.4)	19	26.1 (14.9)		8.3 %	-15.10 [-23.82, -6.38]
Oseid 1995	20	14.1 (9.5)	20	28.9 (18)		7.9 %	-14.80 [-23.72, -5.88]
Roberts 1985	9	18.9 (17.7)	9	38.9 (18.9)		2.4 %	-20.00 [-36.92, -3.08]
Todaro 1993	13	10.1 (8.9)	13	23.5 (4)		18.3 %	-13.40 [-18.70, -8.10]
Subtotal (95% CI)	**216**		**216**			**100.0 %**	**-14.51 [-16.98, -12.04]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.85$, df = 14 (P = 0.62); $I^2 = 0.0\%$							
Test for overall effect: Z = 11.51 (P < 0.00001)							
3 > 4 mg MDI							
Morton 1992	16	15.83 (13.43)	16	38.36 (18.01)		100.0 %	-22.53 [-33.54, -11.52]
Subtotal (95% CI)	**16**		**16**			**100.0 %**	**-22.53 [-33.54, -11.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.01 (P = 0.000060)							



Analysis 2.2. Comparison 2 Dose NCS vs placebo, Outcome 2 Maximum fall PEFR.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 2 Dose NCS vs placebo

Outcome: 2 Maximum fall PEFR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 2 mg or less MDI							
Bundgaard 1988	14	25.9 (11.03)	14	41.3 (16.19)		54.4 %	-15.40 [-25.66, -5.14]
Vilsvik 1988	12	33.8 (16.67)	12	44.2 (14.18)		45.6 %	-10.40 [-22.78, 1.98]
Subtotal (95% CI)	**26**		**26**			**100.0 %**	**-13.36 [-21.27, -5.46]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.37, df = 1 (P = 0.54); I^2 =0.0%							
Test for overall effect: Z = 3.32 (P = 0.00092)							
2 4 mg MDI							
Boner 1989	20	10 (11.03)	20	17.5 (16.19)		15.7 %	-7.50 [-16.09, 1.09]
Bundgaard 1988	14	21.3 (11.03)	14	41.3 (16.19)		13.7 %	-20.00 [-30.26, -9.74]
Henriksen 1988	12	17.81 (14.21)	12	45.2 (19.66)		10.3 %	-27.39 [-41.11, -13.67]
Mihalyka 1988	14	13.2 (12)	14	21.9 (15.3)		13.8 %	-8.70 [-18.89, 1.49]
Novembre 1994f	24	15.04 (7.9)	24	22.46 (15.13)		17.9 %	-7.42 [-14.25, -0.59]
Novembre 1994s	19	9.1 (10.9)	19	19.5 (16.9)		15.1 %	-10.40 [-19.44, -1.36]
Vilsvik 1988	12	15 (11.96)	12	44.2 (14.18)		13.5 %	-29.20 [-39.70, -18.70]
Subtotal (95% CI)	**115**		**115**			**100.0 %**	**-14.98 [-21.62, -8.34]**
Heterogeneity: Tau^2 = 55.24; Chi^2 = 20.28, df = 6 (P = 0.002); I^2 =70%							
Test for overall effect: Z = 4.42 (P < 0.00001)							
3 > 4 mg MDI							
Vilsvik 1988	12	22.4 (17.61)	12	44.2 (14.18)		100.0 %	-21.80 [-34.59, -9.01]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**-21.80 [-34.59, -9.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.34 (P = 0.00084)							

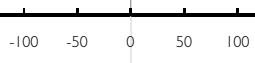
Analysis 3.1. Comparison 3 Different delivery system NCS vs Placebo, Outcome 1 Maximum % fall FEV1.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 3 Different delivery system NCS vs Placebo

Outcome: 1 Maximum % fall FEV1

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 4 mg areosolized NCS using spacer							
Boner 1988	13	7.85 (11.22)	13	16 (17.55)		13.3 %	-8.15 [-19.47, 3.17]
Comis 1993	12	11.6 (6.3)	12	29.3 (15.6)		18.8 %	-17.70 [-27.22, -8.18]
De Benedictis 1994b	8	14.8 (18.6)	8	31.4 (20.6)		4.6 %	-16.60 [-35.83, 2.63]
Novembre 1994f	24	15.42 (8.35)	24	28.46 (13.84)		40.8 %	-13.04 [-19.51, -6.57]
Novembre 1994s	19	11 (12.4)	19	26.1 (14.9)		22.5 %	-15.10 [-23.82, -6.38]
Subtotal (95% CI)	**76**		**76**			**100.0 %**	**-13.89 [-18.02, -9.76]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.82, df = 4 (P = 0.77); I^2 =0.0%							
Test for overall effect: Z = 6.59 (P < 0.00001)							
2 4 mg areosolized NCS regular adapter							
Boner 1988	13	13.54 (13.85)	13	20.77 (21.46)		4.2 %	-7.23 [-21.11, 6.65]
Boner 1989	20	15.7 (13.1)	20	22.7 (16.47)		9.5 %	-7.00 [-16.22, 2.22]
Chudry 1987	12	21.3 (13.1)	12	39.7 (12.9)		7.5 %	-18.40 [-28.80, -8.00]
Comis 1993	12	14.5 (12.2)	12	31.3 (15.1)		6.7 %	-16.80 [-27.78, -5.82]
De Benedictis 1994a	17	14.4 (11.1)	17	27.4 (17.3)		8.5 %	-13.00 [-22.77, -3.23]
De Benedictis 1995	13	15.7 (16.8)	13	29.6 (18.9)		4.3 %	-13.90 [-27.65, -0.15]
Debelic 1986	12	29.83 (15.95)	12	48.08 (15.08)		5.2 %	-18.25 [-30.67, -5.83]
Henriksen 1988	12	17.5 (13.1)	12	47.2 (16.47)		5.7 %	-29.70 [-41.61, -17.79]
Konig 1987	12	12 (14.6)	12	26.2 (12.3)		6.9 %	-14.20 [-25.00, -3.40]
Oseid 1995	20	14.1 (9.5)	20	28.9 (18)		10.1 %	-14.80 [-23.72, -5.88]
Roberts 1985	9	18.9 (17.7)	9	38.9 (18.9)		2.8 %	-20.00 [-36.92, -3.08]
Todaro 1993	13	10.1 (8.9)	13	23.5 (4)		28.7 %	-13.40 [-18.70, -8.10]
Subtotal (95% CI)	**165**		**165**			**100.0 %**	**-14.75 [-17.71, -11.79]**
Heterogeneity: Tau^2 = 1.39; Chi^2 = 11.57, df = 11 (P = 0.40); I^2 =5%							
Test for overall effect: Z = 9.77 (P < 0.00001)							



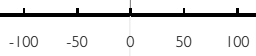
Analysis 3.2. Comparison 3 Different delivery system NCS vs Placebo, Outcome 2 Maximum % fall PEFR.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 3 Different delivery system NCS vs Placebo

Outcome: 2 Maximum % fall PEFR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 4 mg areosolized NCS using spacer							
Novembre 1994f	24	15.04 (7.9)	24	22.46 (15.13)		53.2 %	-7.42 [-14.25, -0.59]
Novembre 1994s	19	9.1 (10.9)	19	19.5 (16.9)		46.8 %	-10.40 [-19.44, -1.36]
Subtotal (95% CI)	**43**		**43**			**100.0 %**	**-8.50 [-13.95, -3.05]**
Heterogeneity: Tau² = 0.0; Chi² = 0.27, df = 1 (P = 0.61); I² =0.0%							
Test for overall effect: Z = 3.06 (P = 0.0022)							
2 4 mg areosolized NCS regular adapter							
Boner 1989	20	10 (11.03)	20	17.5 (16.19)		22.7 %	-7.50 [-16.09, 1.09]
Bundgaard 1988	14	21.3 (11.03)	14	41.3 (16.19)		20.4 %	-20.00 [-30.26, -9.74]
Henriksen 1988	12	17.81 (14.21)	12	45.2 (19.66)		16.2 %	-27.39 [-41.11, -13.67]
Mihalyka 1988	14	13.2 (12)	14	21.9 (15.3)		20.5 %	-8.70 [-18.89, 1.49]
Vilsvik 1988	12	15 (11.96)	12	44.2 (14.18)		20.1 %	-29.20 [-39.70, -18.70]
Subtotal (95% CI)	**72**		**72**			**100.0 %**	**-18.02 [-27.07, -8.97]**
Heterogeneity: Tau² = 77.21; Chi² = 14.96, df = 4 (P = 0.005); I² =73%							
Test for overall effect: Z = 3.90 (P = 0.000095)							



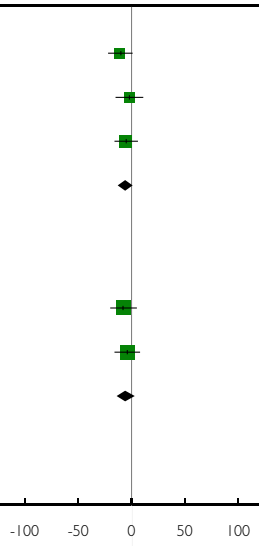
Analysis 4.1. Comparison 4 Duration of action NCS vs placebo, Outcome 1 Maximum fall FEV1.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 4 Duration of action NCS vs placebo

Outcome: 1 Maximum fall FEV1

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 120 - 150 min post treatment							
Chudry 1987	12	25.6 (12.9)	12	36.1 (16.8)		33.5 %	-10.50 [-22.48, 1.48]
De Benedictis 1995	13	23.9 (19.1)	13	25.5 (14.3)		28.6 %	-1.60 [-14.57, 11.37]
Konig 1987	12	23.1 (12.9)	12	28.3 (15.2)		37.8 %	-5.20 [-16.48, 6.08]
Subtotal (95% CI)	**37**		**37**			**100.0 %**	**-5.95 [-12.89, 0.99]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.00$, df = 2 (P = 0.61); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.68 (P = 0.093)							
2 240 - 270 min post treatment							
Chudry 1987	12	26.1 (15.2)	12	33.8 (16)		46.4 %	-7.70 [-20.19, 4.79]
Konig 1987	12	24.3 (13.8)	12	28.2 (15.2)		53.6 %	-3.90 [-15.52, 7.72]
Subtotal (95% CI)	**24**		**24**			**100.0 %**	**-5.66 [-14.17, 2.84]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.31 (P = 0.19)							



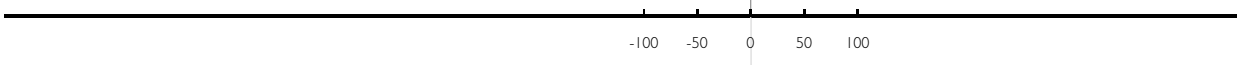
Analysis 5.1. Comparison 5 Severity of EIB, Outcome 1 Maximum % fall FEV1.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 5 Severity of EIB

Outcome: 1 Maximum % fall FEV1

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mild EIB (< 30% maximum fall FEV1)							
Boner 1988	13	13.54 (13.85)	13	20.77 (21.46)		3.1 %	-7.23 [-21.11, 6.65]
Boner 1989	20	15.7 (13.1)	20	22.7 (16.47)		6.6 %	-7.00 [-16.22, 2.22]
De Benedictis 1994a	17	14.4 (11.1)	17	27.4 (17.3)		5.9 %	-13.00 [-22.77, -3.23]
De Benedictis 1995	13	15.7 (16.8)	13	29.6 (18.9)		3.1 %	-13.90 [-27.65, -0.15]
Konig 1987	12	12 (14.6)	12	26.2 (12.3)		4.9 %	-14.20 [-25.00, -3.40]
Novembre 1994f	24	15.42 (8.35)	24	28.46 (13.84)		12.1 %	-13.04 [-19.51, -6.57]
Novembre 1994s	19	11 (12.4)	19	26.1 (14.9)		7.3 %	-15.10 [-23.82, -6.38]
Oseid 1995	20	14.1 (9.5)	20	28.9 (18)		7.0 %	-14.80 [-23.72, -5.88]
Todaro 1993	13	10.1 (8.9)	13	23.5 (4)		16.6 %	-13.40 [-18.70, -8.10]
Subtotal (95% CI)	**151**		**151**			**66.7 %**	**-12.84 [-15.65, -10.03]**
Heterogeneity: Tau² = 0.0; Chi² = 2.74, df = 8 (P = 0.95); I² =0.0%							
Test for overall effect: Z = 8.95 (P < 0.00001)							
2 Moderate-Severe EIB (30% or greater maximum fall in FEV1)							
Chudry 1987	12	21.3 (13.1)	12	39.7 (12.9)		5.3 %	-18.40 [-28.80, -8.00]
Comis 1993	12	14.5 (12.2)	12	31.3 (15.1)		4.8 %	-16.80 [-27.78, -5.82]
De Benedictis 1994b	8	14.8 (18.6)	8	31.4 (20.6)		1.6 %	-16.60 [-35.83, 2.63]
Debelic 1986	12	29.83 (15.95)	12	48.08 (15.08)		3.8 %	-18.25 [-30.67, -5.83]
Henriksen 1988	12	17.5 (13.1)	12	47.2 (16.47)		4.1 %	-29.70 [-41.61, -17.79]
Morton 1992	16	15.83 (13.43)	16	38.36 (18.01)		4.8 %	-22.53 [-33.54, -11.52]
Roberts 1985	9	18.9 (17.7)	9	38.9 (18.9)		2.1 %	-20.00 [-36.92, -3.08]
Shaw 1985	8	10.27 (7.02)	8	34.43 (10.96)		6.9 %	-24.16 [-33.18, -15.14]
Subtotal (95% CI)	**89**		**89**			**33.3 %**	**-21.36 [-25.52, -17.20]**
Heterogeneity: Tau² = 0.0; Chi² = 3.77, df = 7 (P = 0.81); I² =0.0%							
Test for overall effect: Z = 10.07 (P < 0.00001)							
Total (95% CI)	**240**		**240**			**100.0 %**	**-15.64 [-18.14, -13.15]**
Heterogeneity: Tau² = 2.44; Chi² = 17.57, df = 16 (P = 0.35); I² =9%							
Test for overall effect: Z = 12.30 (P < 0.00001)							



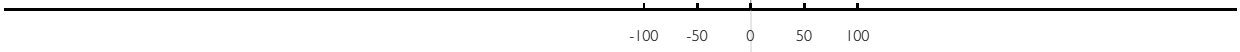
Analysis 5.2. Comparison 5 Severity of EIB, Outcome 2 Maximum % fall PEFR.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 5 Severity of EIB

Outcome: 2 Maximum % fall PEFR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mild EIB (< 30% maximum fall PEFR)							
Boner 1989	20	10 (11.03)	20	17.5 (16.19)		15.4 %	-7.50 [-16.09, 1.09]
Mihalyka 1988	14	13.2 (12)	14	21.9 (15.3)		14.0 %	-8.70 [-18.89, 1.49]
Novembre 1994f	24	15.04 (7.9)	24	22.46 (15.13)		17.0 %	-7.42 [-14.25, -0.59]
Novembre 1994s	19	9.1 (10.9)	19	19.5 (16.9)		15.0 %	-10.40 [-19.44, -1.36]
Subtotal (95% CI)	**77**		**77**			**61.4 %**	**-8.30 [-12.49, -4.10]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.31, df = 3 (P = 0.96); I^2 =0.0%							
Test for overall effect: Z = 3.88 (P = 0.00011)							
2 Moderate-Severe EIB (30% or greater maximum fall in PEFR)							
Bundgaard 1988	14	21.3 (11.03)	14	41.3 (16.19)		13.9 %	-20.00 [-30.26, -9.74]
Henriksen 1988	12	17.81 (14.21)	12	45.2 (19.66)		11.0 %	-27.39 [-41.11, -13.67]
Vilsvik 1988	12	15 (11.96)	12	44.2 (14.18)		13.7 %	-29.20 [-39.70, -18.70]
Subtotal (95% CI)	**38**		**38**			**38.6 %**	**-25.14 [-31.61, -18.67]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.64, df = 2 (P = 0.44); I^2 =0.0%							
Test for overall effect: Z = 7.61 (P < 0.00001)							
Total (95% CI)	**115**		**115**			**100.0 %**	**-14.98 [-21.62, -8.34]**
Heterogeneity: Tau^2 = 55.24; Chi^2 = 20.28, df = 6 (P = 0.002); I^2 =70%							
Test for overall effect: Z = 4.42 (P < 0.00001)							



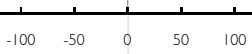
Analysis 6.1. Comparison 6 Effect of time of pretreatment, Outcome 1 maximum % fall FEV1.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 6 Effect of time of pretreatment

Outcome: 1 maximum % fall FEV1

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 < 30 minutes pre-exercise							
Boner 1988	13	13.54 (13.85)	13	20.77 (21.46)		3.1 %	-7.23 [-21.11, 6.65]
De Benedictis 1994a	17	14.1 (11.1)	17	27.4 (17.3)		5.9 %	-13.30 [-23.07, -3.53]
De Benedictis 1994b	8	14.8 (18.6)	8	31.4 (20.6)		1.6 %	-16.60 [-35.83, 2.63]
De Benedictis 1995	13	15.7 (16.8)	13	29.6 (18.9)		3.1 %	-13.90 [-27.65, -0.15]
Konig 1987	12	12 (14.6)	12	26.2 (12.3)		4.9 %	-14.20 [-25.00, -3.40]
Morton 1992	16	15.83 (13.43)	16	38.36 (18.01)		4.8 %	-22.53 [-33.54, -11.52]
Novembre 1994f	24	15.42 (8.35)	24	28.46 (13.84)		12.2 %	-13.04 [-19.51, -6.57]
Novembre 1994s	19	11 (12.4)	19	26.1 (14.9)		7.3 %	-15.10 [-23.82, -6.38]
Shaw 1985	8	10.27 (7.02)	8	34.43 (10.96)		6.8 %	-24.16 [-33.18, -15.14]
Todaro 1993	13	10.1 (8.9)	13	23.5 (4)		16.7 %	-13.40 [-18.70, -8.10]
Subtotal (95% CI)	**143**		**143**			**66.4 %**	**-15.05 [-17.87, -12.22]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.85$, df = 9 (P = 0.55); $I^2 = 0.0\%$							
Test for overall effect: Z = 10.44 (P < 0.00001)							
2 30 minutes or more pre-exercise							
Boner 1989	20	15.7 (13.1)	20	22.7 (16.47)		6.6 %	-7.00 [-16.22, 2.22]
Chudry 1987	12	21.3 (13.1)	12	39.7 (12.9)		5.3 %	-18.40 [-28.80, -8.00]
Comis 1993	12	14.5 (12.2)	12	31.3 (15.1)		4.8 %	-16.80 [-27.78, -5.82]
Debelic 1986	12	29.83 (15.95)	12	48.08 (15.08)		3.8 %	-18.25 [-30.67, -5.83]
Henriksen 1988	12	17.5 (13.1)	12	47.2 (16.47)		4.1 %	-29.70 [-41.61, -17.79]
Oseid 1995	20	14.1 (9.5)	20	28.9 (18)		7.0 %	-14.80 [-23.72, -5.88]
Roberts 1985	9	18.9 (17.7)	9	38.9 (18.9)		2.1 %	-20.00 [-36.92, -3.08]
Subtotal (95% CI)	**97**		**97**			**33.6 %**	**-17.03 [-22.26, -11.80]**
Heterogeneity: $Tau^2 = 17.40$; $Chi^2 = 9.31$, df = 6 (P = 0.16); $I^2 = 36\%$							
Test for overall effect: Z = 6.39 (P < 0.00001)							
Total (95% CI)	**240**		**240**			**100.0 %**	**-15.66 [-18.15, -13.17]**
Heterogeneity: $Tau^2 = 2.35$; $Chi^2 = 17.51$, df = 16 (P = 0.35); $I^2 = 9\%$							
Test for overall effect: Z = 12.34 (P < 0.00001)							



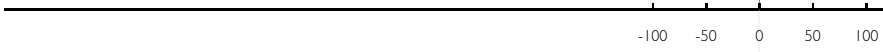
Analysis 6.2. Comparison 6 Effect of time of pretreatment, Outcome 2 maximum % fall PEFR.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

Comparison: 6 Effect of time of pretreatment

Outcome: 2 maximum % fall PEFR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 < 30 minutes minutes pre-exercise							
Mihalyka 1988	14	13.2 (12)	14	21.9 (15.3)		14.0 %	-8.70 [-18.89, 1.49]
Novembre 1994f	24	15.04 (7.9)	24	22.46 (15.13)		17.0 %	-7.42 [-14.25, -0.59]
Novembre 1994s	19	9.1 (10.9)	19	19.5 (16.9)		15.0 %	-10.40 [-19.44, -1.36]
Subtotal (95% CI)	**57**		**57**			**46.0 %**	**-8.55 [-13.35, -3.74]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.27, df = 2 (P = 0.88); I^2 =0.0%							
Test for overall effect: Z = 3.49 (P = 0.00049)							
2 30 minutes or more pre-exercise							
Boner 1989	20	10 (11.03)	20	17.5 (16.19)		15.4 %	-7.50 [-16.09, 1.09]
Bundgaard 1988	14	21.3 (11.03)	14	41.3 (16.19)		13.9 %	-20.00 [-30.26, -9.74]
Henriksen 1988	12	17.81 (14.21)	12	45.2 (19.66)		11.0 %	-27.39 [-41.11, -13.67]
Vilsvik 1988	12	15 (11.96)	12	44.2 (14.18)		13.7 %	-29.20 [-39.70, -18.70]
Subtotal (95% CI)	**58**		**58**			**54.0 %**	**-20.47 [-31.03, -9.91]**
Heterogeneity: Tau^2 = 86.06; Chi^2 = 11.98, df = 3 (P = 0.01); I^2 =75%							
Test for overall effect: Z = 3.80 (P = 0.00015)							
Total (95% CI)	**115**		**115**			**100.0 %**	**-14.98 [-21.62, -8.34]**
Heterogeneity: Tau^2 = 55.24; Chi^2 = 20.28, df = 6 (P = 0.002); I^2 =70%							
Test for overall effect: Z = 4.42 (P < 0.00001)							



Analysis 7.1. Comparison 7 NCS inclusive vs placebo, Outcome 1 mean maximum % fall FEV1.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

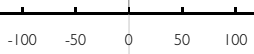
Comparison: 7 NCS inclusive vs placebo

Outcome: 1 mean maximum % fall FEV1

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Todaro 1993	13	10.1 (8.9)	13	23.5 (4)		16.6 %	-13.40 [-18.70, -8.10]
De Benedictis 1994a	17	14.4 (11.1)	17	27.4 (17.3)		5.9 %	-13.00 [-22.77, -3.23]
Konig 1987	12	12 (14.6)	12	26.2 (12.3)		4.9 %	-14.20 [-25.00, -3.40]
De Benedictis 1995	13	15.7 (16.8)	13	29.6 (18.9)		3.1 %	-13.90 [-27.65, -0.15]
Shaw 1985	8	10.27 (7.02)	8	34.43 (10.96)		6.9 %	-24.16 [-33.18, -15.14]
De Benedictis 1994b	8	14.8 (18.6)	8	31.4 (20.6)		1.6 %	-16.60 [-35.83, 2.63]
Boner 1988	13	13.54 (13.85)	13	20.77 (21.46)		3.1 %	-7.23 [-21.11, 6.65]
Novembre 1994s	19	11 (12.4)	19	26.1 (14.9)		7.3 %	-15.10 [-23.82, -6.38]
Novembre 1994f	24	15.42 (8.35)	24	28.46 (13.84)		12.1 %	-13.04 [-19.51, -6.57]
Morton 1992	16	15.83 (13.43)	16	38.36 (18.01)		4.8 %	-22.53 [-33.54, -11.52]
Oseid 1995	20	14.1 (9.5)	20	28.9 (18)		7.0 %	-14.80 [-23.72, -5.88]
Comis 1993	12	14.5 (12.2)	12	31.3 (15.1)		4.8 %	-16.80 [-27.78, -5.82]
Chudry 1987	12	21.3 (13.1)	12	39.7 (12.9)		5.3 %	-18.40 [-28.80, -8.00]
Boner 1989	20	15.7 (13.1)	20	22.7 (16.47)		6.6 %	-7.00 [-16.22, 2.22]
Roberts 1985	9	18.9 (17.7)	9	38.9 (18.9)		2.1 %	-20.00 [-36.92, -3.08]
Debelic 1986	12	29.83 (15.95)	12	48.08 (15.08)		3.8 %	-18.25 [-30.67, -5.83]
Henriksen 1988	12	17.5 (13.1)	12	47.2 (16.47)		4.1 %	-29.70 [-41.61, -17.79]
Total (95% CI)	**240**		**240**			**100.0 %**	**-15.64 [-18.14, -13.15]**

Heterogeneity: $Tau^2 = 2.44$; $Chi^2 = 17.57$, df = 16 (P = 0.35); $I^2 = 9\%$

Test for overall effect: Z = 12.30 (P < 0.00001)



Analysis 7.2. Comparison 7 NCS inclusive vs placebo, Outcome 2 mean maximum % fall PEFR.

Review: Nedocromil sodium for preventing exercise-induced bronchoconstriction

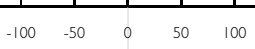
Comparison: 7 NCS inclusive vs placebo

Outcome: 2 mean maximum % fall PEFR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Novembre 1994f	24	15.04 (7.9)	24	22.46 (15.13)		17.0 %	-7.42 [-14.25, -0.59]
Novembre 1994s	19	9.1 (10.9)	19	19.5 (16.9)		15.0 %	-10.40 [-19.44, -1.36]
Mihalyka 1988	14	13.2 (12)	14	21.9 (15.3)		14.0 %	-8.70 [-18.89, 1.49]
Henriksen 1988	12	17.81 (14.21)	12	45.2 (19.66)		11.0 %	-27.39 [-41.11, -13.67]
Boner 1989	20	10 (11.03)	20	17.5 (16.19)		15.4 %	-7.50 [-16.09, 1.09]
Vilsvik 1988	12	15 (11.96)	12	44.2 (14.18)		13.7 %	-29.20 [-39.70, -18.70]
Bundgaard 1988	14	21.3 (11.03)	14	41.3 (16.19)		13.9 %	-20.00 [-30.26, -9.74]
Total (95% CI)	**115**		**115**			**100.0 %**	**-14.98 [-21.62, -8.34]**

Heterogeneity: $Tau^2 = 55.24$; $Chi^2 = 20.28$, df = 6 (P = 0.002); $I^2 = 70\%$

Test for overall effect: Z = 4.42 (P < 0.00001)



WHAT'S NEW

Last assessed as up-to-date: 6 August 2008.

Date	Event	Description
7 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 2, 1998

Date	Event	Description
20 September 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

CH Spooner: initial searches & screening, form design, study selection, quality assessments, author correspondence, statistics, data extraction and entry, primary author. Converted to RevMan4.

LD Saunders: study selection, quality assessments, statistical advice, and editing.

BH Rowe: study selection, quality assessments, statistical advice, editing, and ARG assigned editor.

DECLARATIONS OF INTEREST

None of the reviewers have been involved, in any manner, with the pharmaceutical company responsible for the production and marketing of nedocromil sodium.

SOURCES OF SUPPORT

Internal sources

- Department of Public Health Sciences, University of Alberta, Edmonton, Canada.
- NHS Research and Development, UK.

External sources

- Institute of Health Economics, Edmonton, Alberta, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Anti-Asthmatic Agents [*therapeutic use]; Asthma, Exercise-Induced [*drug therapy]; Bronchoconstriction [*drug effects]; Cross-Over Studies; Nedocromil [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Aged; Humans; Middle Aged