Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction (Review)

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[Intervention Review]

Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

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ABSTRACT

Background

Exercise-induced bronchoconstriction (or asthma) following strenuous physical exertion is common and can cause sub-optimal performance, symptoms such as cough, dyspnea, wheeze, chest tightness, and can lead people to avoid physical activity. Management focuses on prevention with pre-exercise treatment using various pharmacologic agents. Mast cell stabilizing agents are effective in attenuating exercise-induced bronchoconstriction but their effectiveness compared to bronchodilator agents is unclear.

Objectives

To quantitatively compare the effects of inhaling a single dose of either mast cell stabiliser - nedocromil sodium or sodium cromoglycate - to a single dose of short acting beta-agonists or anti-cholinergic agents - atropine or ipratropium bromide - prior to a strenuous exercise challenge in participants with asthma who are at least 6 years of age and suffer from reproducible exercise-induced bronchoconstriction. The review also compares the effects between a short acting beta-agonist alone to a combination of a short acting beta-agonist + mast cell stabiliser.

Search methods

We searched the Cochrane Airways Group Specialised Register, CENTRAL, Current Contents, review articles, textbooks and reference lists of articles. We also contacted the drug manufacturer and primary authors for additional citations. Searches are current as of August 2008.

Selection criteria

Randomised trials comparing a single prophylactic dose of a mast cell stabiliser to a short acting beta-agonist, anti-cholinergic agent, or a short acting beta-agonist alone to a combination of short acting beta-agonist plus a mast cell stabiliser to prevent exercise-induced bronchoconstriction in asthmatics over six years old. The exercise challenge had to conform to acceptable standards and pulmonary function (PFT) reported as percent decrease from baseline of FEV1 or peak flow. Complete protection (maximum % fall PFT <15% post-exercise) and clinical protection (50% improvement over placebo effect) measures were included.

Data collection and analysis

Trial inclusion and quality assessments were conducted independently by two reviewers using standardised forms. A second reviewer confirmed data extraction and calculations. Attempts were made to contact study authors. The pooled estimate involving continuous pulmonary function measures are reported as a weighted mean difference (WMD), dichotomous data as an odds ratio (OR), both with 95% confidence intervals (95%CI) using a random effects model. Heterogeneity tests for pooled results were performed.

Main results

Twenty-four trials (518 participants) conducted in 13 countries between 1976 and 1998 were included. All drugs were effective at attenuating the exercise-induced bronchoconstriction response but to varying degrees even within the same individual. Compared to anti-cholinergic agents, mast cell stabilisers were somewhat more effective at attenuating bronchoconstriction. On average the maximum fall on MCS was reduced to 7.1% compared to 13.8% on AC (WMD = 6.7%; 95% CI: 3.3 to 10.0), provided more individuals with complete protection (73% vs 56%; OR = 2.2; 95% CI: 1.3 to 3.7) and clinical protection (73% vs 52%; OR = 2.7; 95% CI: 1.1 to 6.4). There were no subgroup differences based on age, severity, or study quality, and no adverse effects were reported for either agent group. When compared to short acting beta-agonists mast cell stabilisers were not as effective at preventing deterioration. On average the maximum fall on MCS was 11.2% compared to 4.3% on beta agonists (WMD = 6.8%; 95% CI: 4.5 to 9.2). MCS provided fewer individuals with complete protection (66% vs 85%; OR = 0.3; 95% CI: 0.2 to 0.5) or clinical protection (55% vs 77%; OR = 0.4; 95% CI: 0.2 to 0.8). There were no significant subgroup differences based on age, severity, drug, delivery, or study quality. A non-significant difference in side effects was demonstrated with 11% of short acting beta-agonist patients experiencing side effects compared to 3% of those receiving mast cell stabilisers (OR = 0.2; 95% CI: 0.0 to 8.2). Combining mast cell stabilisers with a short acting beta-agonist did not produce significant advantages to pulmonary function over short acting beta-agonists alone. On average the maximum fall on SABA only was reduced to 5.3% compared to 3.5% on the combination (WMD = 1.8%; 95% CI: -1.1 to 4.6). Beta-agonists alone provided fewer individuals with complete protection (68% vs 80%; OR = 0.5; 95% CI: 0.2 to 1.4) or clinical protection (70% vs 86%; OR=0.4; 95% CI: 0.1 to 1.2) but the difference did not reach significance (p=0.17). There were no subgroup differences.

Authors' conclusions

In a population of stable asthmatics short acting beta-agonists, mast cell stabilisers, or anticholinergics will provide a significant protective effect against exercise-induced bronchoconstriction with few adverse effects. On average, SABAs resulted in more effective attenuation than mast cell stabilisers, while mast cell stabilisers were more effective than anti-cholinergic agents. Combining SABA and mast cell stabilisers may be appropriate in selected cases. The variability in the individual degree of response to these drugs in multi arm trials suggests clinicians and patients work together to identify the most effective prophylactic therapy.

PLAIN LANGUAGE SUMMARY

Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Exercise-induced bronchoconstriction, also commonly called exercise-induced asthma, is associated with symptoms such as cough (locker room cough), wheezing, shortness of breath, and chest tightness following exercise. While an episode is generally self-limiting, it can cause those afflicted to avoid vigorous activity and serious athletes to under-perform by limiting endurance and prolonging recovery time. The combined results from the studies, determined that short-acting beta-agonists inhaled prior to exercise reduced the severity of attacks in both adults and children when compared to mast cell stabilizers alone. In addition, the mast-cell stabilizers were slightly more effective than anticholinergic bronchodilators. Combining short-acting beta-agonists and mast-cell stabilizers was no more effective than the agents administered alone. There were no significant adverse effects reported with the short term use of any of the drugs.

BACKGROUND

Acute transient airway narrowing that most often occurs following strenuous physical exercise is referred to as exercise-induced bronchoconstriction (EIB) or exercise induced asthma (EIA) and was first described nearly 2000 years ago. It occurs in 70% to 90% of people with asthma (Anderson 1985; Randolph 1997), 35 to 40% of people with allergic rhinitis (McCarthy 1989), 10 to 50% of elite athletes (Mehta & Busse 1997; Rundell 2002), and an estimated 12% to 15% of the general population (Spector 1993).

Exercise is one of the most common triggers of an acute asthma attack. The attack is typically provoked by 6 to 15 minutes of continuous exercise of at least 80 to 90% predicted maximum workload (Godfrey 1987; Weiler 1996). Airway hyper-reactivity leads to airway narrowing that results in signs of abnormal pulmonary function tests (PFTs), and symptoms of dyspnea, cough, wheeze, chest tightness, premature fatigue, decreased stamina, and prolonged recovery times. Maximum bronchoconstriction usually occurs 3 to 15 minutes post exercise and subsides spontaneously within 20 to 60 minutes (Virant 1992; Brudno 1994). A post-challenge fall of forced expiratory volume in 1 second (FEV1) of 10 -15% or more is diagnostic of EIB (Beck 1997). Occasionally there is a late phase response (Chhabra 1998) and some people experience a refractory period of up to 3 hours, during which further exercise causes less obstruction (Gotshall 2002).

The severity of the reaction is influenced by several factors - chronic asthma therapy, intensity and duration of activity, environmental conditions, degree of underlying bronchial hyper reactivity, level of physical conditioning, and the time interval since previous exercise (Rupp 1996). A 'rescue' bronchodilator agent may be needed if PFT decreases in excess of 30% occur (Anderson 1985) and episodes can be severe enough to require emergency treatment. Therefore, EIB is a concern not only to those who suffer from it, but also to those who supervise physical activities.

Keeping physically active contributes to healthy physical and social development but those with EIB may avoid participating in triggering activities (including employment choices) or simply suffer because they don't recognize the abnormal response (Massie 2002; Hogshead 1989). Therefore the diagnosis and treatment of EIB is important for achieving healthy self-esteem and maximum physical performance. The benefits of successful management can be remarkable at all ages and levels of activity - with treatment, 67 EIB athletes competing at the 1984 Olympics won 41 medals, 15 of them gold (Pierson 1988).

The complex pathophysiology underlying EIB continues to stimulate debate; however, it is known that EIB cannot be 'cured' (Anderson 2000). Management must focus on prevention, with the aim being symptom free activity. This can be achieved through a combination of pharmacologic and non-pharmacologic interventions. A variety of medications have been shown to prevent or at least reduce the EIB response. The traditional recommendation has been a pre-exercise dose of a short acting bronchodilator (SABA), such as salbutamol (Virant 1992; Sly 1984). Mast-cell stabilizing agents, such as nedocromil sodium (NCS) and sodium cromoglycate (SCG), as well as inhaled anticholinergics have also been recommended. A Cochrane meta-analysis (Spooner 1998) demonstrated that nedocromil sodium had a statistically and clinically significant effect in attenuating EIB. A subsequent meta-analysis, comparing NCS to SCG (Kelly 2000), found no significant difference between the two when examining effects on pulmonary function, complete protection, clinical protection, or side effect profiles.

The present systematic review seeks to examine the available evidence comparing either of these two mast-cell stabilising agents to short-acting bronchodilator therapies for treating EIB. It also looked at lung function when a mast-cell stabiliser was given in combination with a SABA..

OBJECTIVES

The objectives of this review are threefold: 1) to compare the effect of a prophylactic dose of either NCS or SCG (hereafter designated together as mast cell stabilisers or MCS) to that of an anticholinergic agent (atropine or ipratropium bromide; hereafter designated anticholinergics or AC), 2) to compare the effect of prophylactic doses of MCS to short acting beta-agonists (SABA), and 3) to compare the effect of a prophylactic dose of SABA alone to a combination of SABA + MCS prior to a strenuous exercise challenge in participants with asthma who are at least 6 years of age and suffer from reproducible EIB.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials were considered for inclusion. Data published in abstract form only were excluded unless the authors could provide a full manuscript for review. Unpublished data was also considered.

Types of participants

All studies on children (=>6 years) and adults (=>17 years) 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. The selection criteria formally defined EIB as a fall from baseline of 10% or greater in FEV1 or PEFR following exercise although all of the included studies required at least a 15% or 20% fall for inclusion into the individual trials.

Types of interventions

The focus of this review was on trials in which participants were randomised to receive an MCS agent compared to either an AC, a SABA, or a combination of a SABA + MCS in a single prophylactic dose prior to a standardised exercise challenge test sufficient to trigger EIB. If studies had more than one drug arm, only the comparisons with the drugs under study were included (placebo comparisons, and other combinations were excluded). The following were also excluded: studies that involved delivery via nasal sprays, and trials investigating experimental or numbered drugs.

Types of outcome measures

All patient outcomes, both subjective and objective, were considered.

Primary outcomes

The primary outcome of interest was the maximum percent fall in pulmonary function, which is the conventional approach to quantifying EIB (Anderson 1985). The percent (%) fall index expresses the reduction in lung function after exercise as a percent of the pre-exercise baseline. The formula to calculate the fall index was [maximum % fall PFT = (baseline PFT - lowest post-exercise PFT) / baseline PFT x 100].

Secondary outcomes

1. The proportion of participants who received complete protection from EIB. As in other EIB reviews (Spooner 1998; Kelly 2000), a drug was considered to offer complete protection if the maximum % fall index was < 15%.
2. The number of participants who received clinical protection from EIB. As in other EIB reviews (Spooner 1998; Kelly 2000), a drug was considered to offer clinical protection if PFT values improved by 50% or more over the placebo effect (ERS Task Force 1997). The formula used to calculate clinical protection was: [clinical protection = (maximum % fall placebo - maximum % fall drug) / maximum % fall placebo x 100]. (Anderson 1985).
3. The number and nature of adverse effects experienced.
4. Subjective outcomes involving symptom scores or preference measures.

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE 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) AND (beta-agonist* OR "beta agonist*" OR albuterol OR salbutamol OR ventolin OR proventil OR metaproterenol OR alupent OR orciprenalin* OR terbutalin* OR bricanyl OR fenoterol OR reproterol OR procaterol OR anticholinergic* OR atropine OR ipratropium OR atrovent OR Bitolterol OR Tornalate OR Isoetharine* OR Etyprenalinum OR Bronkometer OR Isoetarin OR Pirbuterol OR Pyrbuterol OR Maxair)
The most recent search was carried out in August 2008

Searching other resources

In addition, Current Contents, reference lists of included studies, review articles and textbooks were searched for relevant citations.

Data collection and analysis

Selection of studies

A two-step process was employed to select articles:
Phase 1: Two reviewers independently screened the initial searches of all the databases and reference lists to identify potentially relevant citations using title, abstract +/- MeSH headings.
Phase II: The full text of all selected articles was obtained and, using defined eligibility criteria, two independent reviewers selected trials for inclusion in the review. Appropriate members of the CAG screened foreign language articles and abstracted data if an article qualified. Reviewers were not blinded to authors, journal, results, etc. All articles for which there was agreement were included; discussion or a third party adjudication was used to resolve disagreements when necessary.

Data extraction and management

One reviewer, who used a standard form, extracted data twice and compared results. All data, numeric calculations, and graphic extrapolations were independently confirmed. Reviewers attempted to contact authors for additional papers, confirm data extraction, and to obtain missing data.
Data extraction included the following:
Methods: study design, method of randomisation, withdrawals, definition of EIB, exercise challenge procedure.
Population: Country, recruitment, sample size, age, gender, inclusion and exclusion criteria, mean severity on placebo.
Intervention: delivery device, timing of therapy, agents, dose, and co-intervention.
Outcomes: PFT, protection, ADRs.
Notes: Quality score, statistical issues.

The data were evaluated for publication bias using graphical and statistical methods.

Assessment of risk of bias in included studies

Quality assessment was carried out using the Cochrane system (CC Handbook), which assesses the method of concealment of allocation, and the Jadad 5-point scale that assesses randomisation, blinding, and withdrawals (Jadad 1996). Discussion or a third party adjudication was used to resolve disagreements when necessary.

Data synthesis

Data were entered and analysed using Review Manager (Version 4.1). For continuous variables, a random effects weighted mean difference (WMD) with 95% confidence interval (CI) was calculated for each study. All similar studies were pooled using a random effects model WMD with 95% CI. For dichotomous variables, a random effects odds ratio (OR) with 95% CI was calculated for individual studies. All similar studies were pooled using random effects OR with 95% CI. For pooled effects, heterogeneity was tested using the Breslow-Day test; $p < 0.05$ was considered statistically significant. A random effects model was selected to provide a more conservative estimate of effect. A sensitivity analysis comparing a fixed effects model with a random effects model was performed.

Our primary intent was to provide a pooled estimate of the mean difference in effect on pulmonary function (PFTs) - either FEV1 or PEFR. Secondarily, we wanted to provide a pooled estimate of the mean difference in PFT related to clinical protection (measured in continuous pulmonary function measures); as well a pooled odds ratio (OR) for obtaining clinical protection, a pooled OR for obtaining complete protection from EIB and, finally, a pooled OR for adverse reactions (ADRs). The latter compared as dichotomous measures.

Subgroup analysis and investigation of heterogeneity

Where significant heterogeneity existed, the reviewers performed sensitivity analysis based on methodological quality (high Jadad score 3-5 vs. low <3), and the formula used to calculate the per cent fall index.

Subgroup analyses were conducted for children and adults. The reviewers also explored the impact of delivery method, choice of drug, severity of EIB, and recent steroid use. In keeping with previous reviews, mild EIB was defined as a percent fall index of <30% on placebo, moderate to severe EIB as a percent fall of => 30% (Spooner 1998; Kelly 2000). When individual patient data were available, the outcomes were calculated from this data and participants who did not demonstrate EIB on placebo were omitted. Though a fall in pulmonary function of 10% is suggestive of EIB, all trialists elected to set their inclusion criteria at 15% or greater; therefore, we used a fall of < 15% post exercise to indicate complete protection.

RESULTS

Description of studies

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

Results of the search

Seventy-eight 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 eighty-two potentially relevant studies. From the title, abstract, and keywords, two reviewers independently selected 41 (50%) for full text review (kappa 0.92). Nine foreign language studies were screened by CAG members. Searches are updated annually. The last updated search was performed in August 2008. Twenty-four trials are included in this review.

Included studies

Twenty-four studies met the inclusion criteria, 3 were foreign language trials. Collectively, they reported data on 518 participants (M=251; F=162; 7 did not report gender distribution). Thirteen trials studied children age 6-17, while the remaining 11 studied adults 18 or older. Sixteen trials were classified as severe EIB (% fall PFT on placebo => 30%) while 7 were considered mild EIB and 1 did not report this information. Five trials reported a total of 13 withdrawals for reasons of no EIB on a test run, an asthma exacerbation at time of testing, or a severe response to a non-included drug; all studies excluded withdrawals from their analysis. The exercise challenges involved an inclined treadmill (N= 19), free running (N=1), bicycling (N=3) and stair climbing (N= 1). All were standardised and met recommended testing criteria (Eggleston 1972). Since all but 2 studies used the cross-over design (2 were parallel: Rohr 1987; Vazquez 1984), all participants received all treatments, the total number of participants listed on the MetaView summary screen is nearly double the actual number of participants.

The 24 trials were conducted between 1976 and 1998 in 12 different countries: 3 North America, 17 Europe, 2 Asia, and 2 Australia. Eleven studies compared an MCS to an AC agent. The mast cell stabilising agent most frequently used was sodium cromoglycate (N = 23, dose range 2 - 40mg; 14 used 20mg); one study used 4 mg nedocromil sodium (de Benedictis 1998). The anticholinergic agent of choice was ipratropium bromide (N=8; dose range 120ug

- 2 mg); 2 studies (Godfrey 1975; Tashkin 1977) employed atropine 0.2% and 1 (Neijens 1981a) oxytropium bromide 0.02mg. Twenty studies compared a MCS to a SABA. All used SCG, but several SABAs were tested: 6 fenoterol (dose range 0.1-2mg), 10 salbutamol (dose range 0.2 -2.5mg), 2 terbutaline, 1 reproterol,1 procaterol and 1 isoproterenol. Ten studies compared a SABA to a combination of SCG + SABA. Four studies used fenoterol, 3 salbutamol, 1 terbutaline, and 1 reproterol. The delivery methods also varied (8 nebulised, 5 MDI, 3 spinhaler, and 2 not described) and six studies employed two or more devices. Due to the wide variety in methods used, post-hoc subgroups were created by SABAs used and delivery method to explore the possible effect on outcome. In all cases, there were interesting observations; however, there were too few studies in each category to draw definitive conclusions.
We also performed a post hoc comparison between studies that included inhaled corticosteroid (ICS) users vs. those that excluded all steroid use in at least the past two weeks. The frequency of regular vs. as needed SABA use prior to testing was not reported and therefore not explored. All studies required participants to abstain from taking any bronchodilator for at least 8 hours prior to a challenge, other medications were withheld for longer periods of time.

Current asthma medication use

Fourteen of the 24 included trials either excluded or reported that participants were not using oral or inhaled corticosteroids at the time of testing. In six studies steroid use was unclear and the total reported use of ICS in four other studies was 14/49 (29%). Some participants were on theophylline or SCG as well as 'as needed SABA use'. No mention of long acting beta-agonist (LABA) use was reported. All studies required patients to discontinue all current asthma medications using adequate washout periods prior to all challenges. The times recommended for washout of asthma medications are: SABA 6hr. , LABA 24 hr., short acting antihistamines 48hr., long acting antihistamines 1 wk., MCS 6 hr., and up to a few days for inhaled steroids (Beck 1997; Anderson 1995).

Pulmonary function outcomes

Sixteen trials (9 children, 7 adult) reported the response to treatment using FEV1 (max % fall FEV1=14; % predicted=1; change= 1); 8 trials (5 children, 3 adult) used PEFR (max % fall PEFR). Studies were not consistent in reporting all of the outcomes of interest and therefore comparisons combine different numbers of studies. Since the majority of studies reported a percent change from baseline rather than absolute PFT values this review provides pooled estimates of FEV1 and PEFR results using a WMD, random effects model. (Percent change was calculated as {baseline PFT - lowest post exercise PFT/baseline PFT * 100%}). The six trials conducted by A. Bundgaard and colleagues on independent participants calculated a top-bottom index (TBI using the formula {TBI = highest PFT prior to, during or immediately after challenge - lowest PFT post-challenge/ highest PFT before/after challenge} (Bundgaard 1983p). Since this formula consistently provides a higher percent change, they were analysed separately to avoid biasing results and over-estimating the pooled result. One trial (Zanconato 1990) measured the energy cost of running, gas exchange and ventilation. One study only reported Jones Lability Index results (Rasmussen 1979) and these are not included in the analyses.

Risk of bias in included studies

Using the Cochrane criteria to assess allocation concealment, 3 studies 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), 5 rated 4 (very good), 9 rated 3 (good), 5 rated 2 (poor), and 3 rated 1 (very poor). All studies stated they were randomised; 16 were double-blinded, 5 were evaluator-blind and 3 did not mention blinding. All authors either described dropouts or had none. Most studies lacked a sufficient description of the method of randomisation and/or blinding used.

Effects of interventions

The results will be reported based on the comparisons articulated in the objectives section above.

Mast cell stabiliser (NCS or SCG) compared to anticholinergic (AC) agents:

Both MCS and AC agents attenuated the EIB response in the majority of participants; however, MCS afforded a modest advantage over AC. From 8 trials (n = 183) the mean maximum fall in post exercise PFT on MCS decreased to 7.1% compared to 13.8% on AC (WMD = 6.7; 95% CI: 3.3 to 10.0%, Analysis 1.1).
Though subgroup comparisons by age and severity favoured MCS, the pooled results between groups were not significantly different:
1. Children vs. adults: the mean maximum fall on MCS in children (n=55) was 9.4% compared to 16.0% on AC (WMD = 6.6%; 95% CI: 1.0 to 12.2%) while the mean maximum fall on MCS in adults (n=128) was 5.8% compared to 12.5% on AC (WMD = 6.7%; 95% CI: 2.5 to 11.0).
2. Mild vs. moderate-severe EIB: the mean maximum fall on MCS in mild EIB (n=125) was 4.7% compared to 10.6 % on AC (WMD = 5.9%; 95% CI: 2.0 to 9.8%) while the mean maximum fall on MCS in moderate-severe EIB (n=58) was 14.2% compared to 23.4% on AC (WMD = 9.1%; 95% CI: 2.3 to 15.9).
3. Non-steroid users: the mean maximum fall on MCS (n=56) was 11.2% compared to 19.5% on AC (WMD = 8.4%; 95% CI: 2.5 to 14.3%) The 3 remaining trials in this group of 8 did not

report current steroid use and so could not be included in the comparison.
Significantly more participants obtained complete protection on MCS (73%) than AC (56%) agents (OR = 2.2; 95% CI: 1.3 to 3.7). The advantage in obtaining clinical protection was also significant, 73% for MCS compared to 52% for AC (OR = 2.7; 95% CI: 1.1 to 6.4). There were no adverse effects reported in either group.

MCS compared to SABA agent:

MCS and SABA also attenuated the EIB response in the majority of participants. In these comparisons SABAs were somewhat more effective at attenuating bronchoconstriction than MCS. From 12 trials (n = 271), the mean maximum fall in post exercise PFT using MCS was 11.2% compared to 4.3% on SABA (WMD = 6.8%; 95% CI: 4.5 to 9.2%, Analysis 2.1). The pooled result from the 5 studies that calculated a TBI also favoured SABA (WMD = 14.7%; 95% CI: 9.1 to 20.3%).
The subgroup comparison by age favoured SABA but the pooled results between groups was not significantly different. The mean maximum fall on MCS in children (n=91) was 11.9% compared to 4.6% on SABA (WMD = 7.3%; 95% CI: 3.9 to 10.7%) while the mean maximum fall on MCS in adults (n=180) was 10.0% compared to 3.5% on SABA (WMD = 6.4%; 95% CI: 2.7 to 10.1).
The subgroup comparison by severity of EIB indicates that participants with more severe EIB obtain a greater benefit from SABAs than MCS compared to those with milder EIB. The mean maximum fall on MCS in mild EIB (n=136) was 7.5% compared to 3.5% on SABA (WMD = 4.0%; 95% CI: 1.7 to 6.4%) while the mean maximum fall on MCS in moderate-severe EIB (n=135) was 16.2% compared to 5.4% on SABA (WMD = 10.8%; 95% CI: 2.3 to 15.9). The difference between these groups was statistically significant. The participants in the four TBI studies were all classified as moderate-severe (n =65), this WMD = 15.3%; 95% CI: 8.1 to 22.3.
Four trials included only non-steroid users, five did not report steroid use, and in the three remaining trials 26% of participants were taking regular inhaled corticosteroids. The mean maximum fall in non-steroid users on MCS (n=78) was 13.1% compared to 6.7% on SABA (WMD = 6.4%; 95% CI: 3.2 to 9.5%). Since no trials included 100% inhaled steroid users no comparison could be made.
Significantly more participants obtained complete protection using SABA (85%) compared to MCS (66%) agents (OR for MCS = 0.3; 95% CI: 0.2 to 0.5). The difference in obtaining clinical protection also significantly favoured SABA over MCS, 77% vs 55% (OR for MCS = 0.4; 95% CI: 0.2 to 0.8). SABA afforded a mean degree of clinical protection over the placebo response that was 23% greater than MCS agents (WMD: 22.7%; 95% CI: 11.9 to 33.4%). SABA caused significant bronchodilation immediately prior to exercise especially in those with lower lung function at baseline whereas MCS did not.
Comparison 2, outcome 9 provides results by beta-2-agonist subgroup, and outcome 8 compares results by delivery method. Although there are some variations in the pooled results, they are not significant and there are not enough studies in all categories to draw any firm conclusions regarding which drug or delivery method is more effective. Adverse or unpleasant effects were noted in 17/152 (11%) after SABA compared to 4/152 (3%) after MCS. The test for heterogeneity was non-significant for all pooled comparisons, except the ones using the TBI.

SABA compared to combination SABA + SCG:

No statistically or clinically significant advantage was identified when SABA alone was compared to a combination of SABA + MCS; however, in all but one study the point estimate favoured the combination. In 5 trials (n=65) using the percent change index, the mean maximum fall PFT WMD = 1.8%; 95% CI: -1.1 to 4.6%). Using the TBI (4 trials), the pooled WMD =13.4 (95% CI: 7.0 to 19.8%). There were not enough studies in each of the subgroups to draw definite conclusions but the results available indicate no significant differences in comparisons by age (children WMD = 1.8%; 95% CI: -1.3 to 4.9% vs adult WMD = 1.3%; 95% CI: -6.3 to 28.9), or severity (mild EIB WMD = 1.5%: 95% CI: -1.5 to 4.5% vs moderate-severe EIB WMD = -0.5%; 95% CI: -3.3 to 2.3%). Seventy percent of participants obtained clinical protection on SABA alone versus 86% on the combination (OR = 0.4; 95% CI: 0.1 to 1.2). Complete protection was obtained in 68% on SABA compared to 80% using the combination (OR = 0.5; 95% CI: 0.2 to 1.4).
The test for heterogeneity was non-significant for all pooled comparisons, and the results remained stable in sensitivity analyses on quality and fixed versus random effects.

Other outcomes

Zanconato et al measured the work effort involved during the exercise challenge (Zanconato 1990). They reported that both SCG and SABA significantly decreased the energy cost of running, ventilation, oxygen consumption, and tidal volume, and therefore significantly increased the running duration. There was no advantage in one drug over the other in this regard. The authors concluded that asthmatics have higher energy requirements per unit of work when untreated compared to treatment with either agent.
An insufficient number of trials reported the time course of EIB in a consistent manner to compare drugs on the basis of recovery time. No trial reported symptom scores.

DISCUSSION

The aim of treatment in EIB is to permit people with asthma to participate in vigorous physical activity and perform at normal or even extraordinary levels without hindrance or lingering symptoms. Several individual studies have been conducted to examine the efficacy of single or combined drugs to attenuate the increased airway resistance caused by exercise. Though some are effective, no one medication has been shown to consistently eliminate EIB. The variability in response within and between individuals at differing times and under circumstances reflects the still poorly understood, complex underlying pathophysiology of EIB (Anderson 2000). To date no large study has been performed to compare the most popular of the treatments - bronchodilators and MCS. This review was designed to determine the efficacy and magnitude of these therapies by performing a systematic review of all trials that compared the effects on pulmonary function of three frequently used inhaled drugs - mast cell stabilizers, anticholinergics, short acting beta 2 agents (plus a combination of SABA and MCS).

This meta-analysis of 24 randomised, crossover trials involving 518 adults and children, across 12 countries, over 18 years, provides further support for the use of a single dose of any of the three drugs as a safe and effective pharmaceutical treatment in EIB. 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% (Beck 1997). None of the participants in these studies were on oral steroids and only 29% were reported to be on inhaled steroids. It is important to remember that although inhaled steroid use usually reduces the severity, significant EIB can still occur in up to 55% of asthmatics well controlled with ICS use and also those with normal lung function at rest (Anderson 1995).

In the comparison of MCS (all used cromoglycate) and anticholinergics (6/9 used ipratropium bromide) the mean maximum fall in pulmonary function was attenuated to less than 15% (7.1% vs. 13.8 % respectively) and the pooled estimate demonstrated that MCSs offer an advantage in the magnitude of 7% (95% CI: 3.3 to 10.0). Whether this degree of improvement was noticed by the participants is not known as preference was not reported in any of the trials. Pooled results showed that 73% vs. 56% obtained complete protection and 73% vs. 52% received clinical protection from MCS over AC. No significant heterogeneity was evident among the pooled trials despite different devices, drugs, doses and timing. Similarly, subgroup analyses based on age and severity failed to identify significant differences between these two medications. Since both categories of drugs do offer complete protection to a large number of people, either would be suitable to recommend based on individual preference.

This meta-analysis also demonstrated that SABAs provide a statistically significant advantage in the percent fall index over MCS in the order of 7% (95% CI: 4.5 to 9.2) though again on average both drugs attenuated the maximum fall to less than 15% (4.3% vs. 11.2% respectively). The response varied little with age, drug, dose, delivery device, or method of calculating the percent falls. Those with more severe EIB did appear to obtain more pulmonary benefit from SABAs over MCS in that the WMD was 4.1% (95% CI:1.7 to 6.4%) in mild EIB and 10.8% (95% CI: 7.4 to 14.2%) in more severe cases. It was not reported whether participants detected this difference or that it affected recovery. The pooled results of nine trials showed 85% received complete protection and 77% clinical protection from SABA compared to 66% and 55% for MCS respectively. Adding a MCS to a SABA may offer a small advantage to some. The pooled estimates of percent fall index or top-bottom index did not indicate any significant differences over a SABA alone and although 80 vs. 68% obtained complete protection this difference was not significant (p=0.46). Twelve studies monitored adverse reactions but only two recorded any. Trials using SABAs did report more side effects (11% vs. 3%, N = 2); however, these were limited to tremor and 'distress' and no patients were forced to withdraw on these grounds. It is hoped that future studies will include measures of preference, symptoms, performance, endurance, etc.

Methodological limitations

As with any meta-analysis, the possibilities of publication and selection biases should be considered. A comprehensive search of published literature for potentially relevant studies was conducted, and attempts were made to contact first authors to identify unpublished work. Often publication bias exists when negative trials, indicating no significant differences between drugs, are not published and thus are not included in a review. Many of the trials included in this review did not demonstrate a significant difference between agents. Although it is possible that a selection bias occurred, we employed two independent reviewers for the selection process. We are confident that the studies excluded were done so for appropriate reasons and in a consistent manner.
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 greater than 70% predicted yet exhibited 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.
3. It is not known how physically fit the participants were.
4. Analyses adjusting for known confounding factors was not possible due to insufficient data. The studies did not provide data or stratify participants based on long term use of anti-

inflammatories such as inhaled steroids or MCS, frequency of prior SABA use for EIB, or long acting beta agonist use.

5. The small number of studies in subgroup categories introduces a note of caution, but the concordance among results is reassuring.

6. Most studies in this review used the 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 the agents used are short acting with rapid clearance and few side effects, we believe the potential for carry-over to be negligible. The majority of exercise challenges were conducted on separate days.

7. 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)

8. All studies were analysed as though they were parallel studies rather than crossover. This along with using a random effects method should ensure that the pooled estimates and confidence intervals are conservative rather than exaggerated .

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

large degree, individualized treatment needs to be developed for each patient using an N of 1 trial approach.

1) Of the three drug categories reviewed (SABAs, mast cell stabilisers, anticholinergics) SABAs appear to be the most effective over a short duration. Overall, complete protection was experienced by 81% with SABAs, 69% with MCS, and 56% with anticholinergics. SABAs produced a small increase in side effects, which may be annoying but not harmful to the user. The current debate of tolerance to SABA with frequent use was not addressed but must be considered. When EIB is severe enough to require treatment SABAs are clearly the treatment of choice and Dr. Anderson suggests reserving them for rescue purposes if other medications work for an individual (Anderson 1995). MCS can be used many times a day without fear of side-effects or tolerance (Kuzemo 1989).

2) Combining a SABA and MCS prior to exercise may provide additional benefit to some, but not to all people with EIB.

Implications for research

Future research should focus on:

1. Correlating pulmonary benefits with patient preference, symptom scores, endurance and recovery time.

2. Validating the duration of response in both responders and non-responders to each drug.

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

4. Conducting randomised trials that stratify participants by long term antiinflammatory use or short and long acting beta-agonist use.

5. Determining whether frequent use leads to developing tolerance.

6. Measuring the energy cost of exercise such as in the Zoncato study (Zanconato 1990).

AUTHORS' CONCLUSIONS

Implications for practice

EIB is a complex pathophysiological phenomenon and response to therapy is difficult to predict with certainty. Having normal or even better than normal lung function (trained athletes) at baseline is not a guarantee that severe EIB will not be experienced. Weather conditions, air quality, personal fitness, physical effort , duration, and underlying bronchial hyper reactivity all influence EIB. To a

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REFERENCES

References to studies included in this review

Boner 1987 *{published data only}*

* Boner AL, Antolini I, Andreoli A, De-Stefano G, Sette L. Comparison of the effects of inhaled calcium antagonist verapamil, sodium cromoglycate and ipratropium bromide on exercise-induced bronchoconstriction in children with asthma. *European Journal of Pediatrics* 1987;**146**:408–11.

Boulet 1889 *{published data only}*

Boulet LP, Turcotte H, Tennina S. Comparative efficacy of salbutamol, ipratropium, and cromoglycate in the prevention of bronchospasm induced by exercise and hyperosmolar challenges. *Journal of Allergy & Clinical Immunology* 1989;**83**(5):882–7.

Bundgaard 1980 *{published data only}*

Bundgaard A, Rasmussen FV, Madsen L. Pretreatment of exercise-induced asthma in adults with aerosols and pulverized tablets. *Allergy* 1980;**35**(8):639–45.

Bundgaard 1983a *{published data only}*

* Bundgaard A, Schmidt A. Pretreatment of exercise-induced asthma by disodium cromoglycate and fenoterol. *European Journal of Respiratory Diseases - Supplement* 1983; **64**(Suppl 128):521–5.

Bundgaard 1983p *{published data only}*

Bundgaard A, Buch D, Schmidt A, Bach-Mortensen N. Pretreatment of exercise-induced asthma in children using disodium cromoglycate and fenoterol inhalation powder. *European Journal of Respiratory Diseases* 1983, (Suppl 130): 36–41.

Bundgaard 1986neb *{published data only}*

* Bundgaard A. Exercise-induced asthma. *European Journal of Respiratory Diseases* 1980;**68**(Suppl 143):51–6.

Bundgaard 1986pdr *{published data only}*

Bundgaard A. Exercise-induced asthma. *European Journal of Respiratory Diseases* 1980;**68**(Suppl 143):51–6.

Clarke 1990 *{published data only}*

* Clarke PS, Ratowsky DA. Effect of fenoterol hydrobromide and sodium cromoglycate individually and in combination on postexercise asthma. *Annals of Allergy* 1990;**64**:187–9.

de Benedictis 1998 *{published data only}*

* de Benedictis FM, Tuteri G, Pazzelli P, Solinas LF, Niccoli A, Parente C. Combination drug therapy for the prevention of exercise-induced bronchoconstriction in children. *Annals of Allergy, Asthma, & Immunology* 1998;**80**(4):352–6.

Debelic 1988 *{published data only}*

Debelic M, Hertel G, Konig J. Double-blind crossover study comparing sodium cromoglycate, reproterol, reproterol plus sodium cromoglycate, and placebo in exercise-induced asthma. *Annals of Allergy* 1988;**61**:25–9.

Dorward 1982 *{published data only}*

Dorward AJ, Patel KR. A comparison of ketotifen with clemastine, ipratropium bromide and sodium cromoglycate in exercise-induced asthma. *Clinical Allergy* 1982;**12**: 355–61.

Gehrke 1986 *{published data only}*

Gehrke I, Bohm E, Sybrecht GW. Stress-induced asthma--placebo-controlled double-blind comparison of prevention using fenoterol, disodium cromoglycate and a combination of the two [Belastungsinduziertes Asthma—-plazebokontrollierter Doppelblind–Vergleich der Pravention mit Fenoterol, DNCG und der Kombination von beiden]. *Prax und Klinik der Pneumologie* 1986;**40**(4): 129–34.

Godfrey 1975 *{published data only}*

Godfrey S, Konig P. Suppression of exercise-induced asthma by salbutamol, theophylline, atropine, cromolyn, and placebo in a group of asthmatic children. *Pediatrics* 1975; **56**:930–4.

Godfrey 1976 *{published data only}*

* Godfrey S, Konig P. Inhibition of exercise-induced asthma by different pharmacological pathways. *Thorax* 1976;**31**: 137–43.

Neijens 1981a *{published data only}*

Neijens HJ, Wesselius T, Kerrebijn KF. Exercise-induced bronchoconstriction as an expression of bronchial hyperreactivity: a study of its mechanisms in children. *Thorax* 1981;**36**:517–22.

Obata 1993 *{published data only}*

Obata T, Matsuda S, Akasawa A, Iikura Y. Preventive effect and duration of action of disodium cromoglycate and procaterol on exercise-induced asthma in asthmatic children. *Annals of Allergy* 1993;**70**(2):123–6.

Pichaipat 1995 *{published data only}*

Pichaipat V, Tongpenyai Y, Nerntong T, Sriprapachiranont C. The protective effect of inhaled terbutaline, sodium cromoglycate and budesonide on exercise-induced asthma in children. *Journal of the Medical Association of Thailand* 1995;**78**(10):505–8.

Rohr 1987 *{published data only}*

Rohr AS, Siegel SC, Katz RM, Rachelefsky GS, Spector SL, Lanier R. A comparison of inhaled albuterol and cromolyn in the prophylaxis of exercise-induced bronchospasm. *Annals of Allergy* 1987;**59**:107–9.

Spada 1985 *{published data only}*

* Spada EL, Donner CF, Meriggi A, Vecchio C. Pharmacological prevention of exercise-induced asthma [Prevenzione farmacologica dell'asma indotto da esercizio fisco]. *Minerva Pneumologica* 1985;**24**:159–64.

Svenonius 1988 *{published data only}*

* Svenonius E, Arborelius M, Wiberg R, Ekberg P. Prevention of exercise-induced asthma by drugs inhaled from metered aerosols. *Allergy* 1988;**43**(4):252–7.

Thompson 1978 *{published data only}*

Thompson NC, Patel KR, Kerr JW. Sodium cromoglycate and ipratropium bromide in exercise-induced asthma. *Thorax* 1978;**33**:694–9.

Tullett 1982 *{published data only}*
* Tullett WM, Patel KR, Berkin KE, Kerr JW. Effect of lignocaine, sodium cromoglycate, and ipratropium bromide in exercise-induced asthma. *Thorax* 1982;**37**:737–40.

Vazquez 1984 *{published data only}*
Vazquez C, Fidalgo I, Virto MC, Labayru MT, Casas C. Efficacy of disodium cromoglycate, salbutamol and ipratropium bromide on the inhibition of exercise-induced bronchospasm [Efectividad del cromoglicato disodico, salbutamol y bromuro de ipratropio en la inhibicion de broncospasmo inducido por ejercicio normales]. *Anales Espanoles de Pediatria* 1984;**20**(8):756–62.

Woolley 1990 *{published data only}*
Woolley M, Anderson AD, Quigley BM. Duration of protective effect of terbutaline sulfate and cromolyn sodium alone and in combination on exercise-induced asthma. *Chest* 1990;**97**:39–45.

Zanconato 1990 *{published data only}*
Zanconato S, Baraldi E, Santuz P, Magagnin G, Zacchello F. Effect of inhaled disodium cromoglycate and albuterol on energy cost of running in asthmatic children. *Pediatric Pulmonology* 1990;**8**(4):240–4.

References to studies excluded from this review

Bauer 1979 *{published data only}*
Bauer X. Concerning the therapy of exercise-induced asthma [Ur Therapie Des Belastungsinduzierten Asthma Bronchiale]. *Praxis und Klinik der Pneumologie* 1979;**33**(6): 791–5.

Bauer 1981 *{published data only}*
* Baur X. Bronchial asthma induced by exercise. *Deutsch Medizinische Wochenschrift* 1981;**106**(10):301–4.

Boner 1984 *{published data only}*
* Boner AL, Zamo CR, Marchiori MM, Biancotto R. Comparison of nebulized ipratropium, salbutamol and cromoglicate solutions, cromoglicate inhaled powder, theophylline elixir and placebo in exercise induced asthma of the children [Confronto fra Nebulizzazione di Ipratropio, Salbutamolo E Cromoglicato In Soluzione, Cromoglicato In Polvere Inalabile, Teofillina Elisir E Placebo Nell'asma Da Esercizio Dei Bambini]. *Giornale Italiano Delle Malattie del Torace* 1984;**38**(6):395–9.

Bundgaard 1983 *{published data only}*
Bundgaard A. Exercise-induced asthma - laboratory observations. *European Journal of Respiratory Diseases* 1983; **64**(Suppl 128):253–7.

Ceugniet 1997 *{published data only}*
Ceugniet F, Cauchefer F, Fragneaud C, Evano-Celli I. Prophylactic treatment of exercise-induced asthma in children: Salmeterol or sodium cromoglycate single dose before exercise? [Traitment preventif de l'asthme induit par l'exercise chez le grand enfant: salmeterol ou cromoglycate de sodium en dose unique avant l'effort?]. *Annales de Pediatrie* 1997;**44**(9):625–34.

Cummings 1984 *{published data only}*
Cummings NP, Strunk RC. Combination drug therapy in children with exercise-induced bronchospasm. *Annals of Allergy* 1984;**53**(5):395–400.

De Cree 1980 *{published data only}*
De Cree J, Verhaegen H, Geukens H. The comparative effects of oxatomide, placebo and sodium cromoglycate. *Clinical Trials Journal* 1980;**17**(3):84–91.

Eggleston 1972 *{published data only}*
Eggleston PA, Bierman CW, Pierson WE, Stamm SJ, Van Arsdel PP. A double-blind trial of the effect of cromolyn sodium on exercise-induced bronchospasm. *Journal of Allergy and Clinical Immunology* 1972;**50**(1):57–63.

Gimeno 1985 *{published data only}*
* Gimeno F, van Veenen R, Steenhuis EJ, Berg WC. Comparison of disodium cromoglycate, terbutaline and thiazinamium in the prevention of exercise-induced asthma and its relation to non-specific bronchial responsiveness. *Respiration* 1985;**48**(2):108–15.

Guerin 1992 *{published data only}*
Guerin JC, Brambilla C, Godard P, De Muizon H, Aubert B, Bons J. Prolonged protection against exercise-induced bronchoconstriction: Salmeterol as compared to sodium cromoglycate [Protection prolongee du bronchospasme a l'effort: salmeterol versus cromoglycate de sodium]. *Revue des Maladies Respiratoires* 1992;**9**(Suppl 1):R27–R30.

Johnson 1986 *{published data only}*
Johnson CE, Belfield PW, Davis S, Cooke NJ, Spencer A, Davies JA. Platelet activation during exercise induced asthma: effect of prophylaxis with cromoglycate and salbutamol. *Thorax* 1986;**41**:290–4.

Joppich 1987 *{published data only}*
* Joppich R. Comparison of the effects of Reproterol, oxitropiumbromide, DNCG, and theophylline in the treatment of exercise induced bronchoconstriction [Vergleich der wirkungen von reproterol, oxitropoiumbromid, DNCG und theophyllin auf das anstrengungs–asthma bei kinder]. *Atemweg und Lungenkrankheiten* 1987;**13**(9):453–6.

Neijens 1981b *{published data only}*
* Neijens HJ, Wesselius TR, Kerrebijn KF. Pharmacologic modification of effort dyspnea in children with CARA [Farmacologische beinvloeding van kortademigheid door inspanning bij kinderen met CARA Farmacologische beinvloeding van kortademigheid door inspanning bij kinderen met CARA]. *Nederlands Tijdschrift voor Geneeskunde* 1981;**125**(32):1277–81.

Rachelefsky 1978 *{published data only}*
Rachelefsky GS, Tashkin DP, Katz RM, Kershnar H, Siegel SC. A comparison of aerosolized atropine, isoproterenol, atropine plus isoproterenol, disodium cromoglycate and placebo in the prevention of exercise-induced asthma. *Chest* 1978;**73**(Suppl 6):1017–19.

Rasmussen 1979 *{published data only}*
* Rasmussen FV, Madsen L, Bundgaard A. Combined effect of an anticholinergic drug ipratropium bromide

and disodium cromoglycate in exercise induced asthma. *Scandinavian Journal of Respiratory Disease* 1979, (Suppl 103):159–62.

Ringel 1982 ***{published data only}***

* Ringel KP, el Nur AR, Karg F. FPL 52758 and disodium cromoglycate (INTAL) in exercise-induced infantile bronchoconstriction. *Zeitschrift fur Erkrankungen der Atmungsorgane* 1982;**159**(1):50–6.

Spada 1984 ***{published data only}***

Spada EL, Donner CF, Fracchia C, Ioli F, Patessio A, Vecchio C. A comparative evaluation of salbutamol, disodium cromoglycate and ipratropium bromide in preventing exercise-induced asthma (EIA). *Respiration* 1984;**46**(Suppl 1):56.

Tabas 1985 ***{published data only}***

Tabas A, Rodriguez A, Lobera T, Dieguez I, Oehling A. Carbuterol, salbutamol and DSCG in exercise-induced asthma. *Allergologia et Immunopathologia* 1985;**13**(6): 493–500.

Tashkin 1977 ***{published data only}***

Tashkin DP, Katz RM, Kerschnar H, Rachelefsky GS, Siegel SC. Comparison of aerosolized atropine, isoproterenol, atropine plus isoproterenol, disodium cromoglycate and placebo in the prevention of exercise-induced asthma. *Annals of Allergy* 1977;**39**:311–8.

Verini 1983 ***{published data only}***

Verini M, Chiarelli F, Di Tullio A, Morgese G, Pallotta R. Pharmacological prevention of exercise-induced bronchospasm. Analysis of literature and evaluation of disodium cromoglycate, fenoterol and ipatroprium bromide in a group of children. *La Pediatria Medica e Chirurgica* 1983;**5**:501–10.

Woolley 1988 ***{published data only}***

Woolley MJ. The duration of action of terbutaline and sodium cromoglycate alone and in combincation on exercise-induced asthma (EIA). *Australian and New Zealand Journal of Medicine* 1988;**18**(3):538.

Additional references

Anderson 1985

Anderson SD. Issues in exercise-induced asthma. *Journal of Allergy & Clinical Immunology* 1985;**76**(6):763–72.

Anderson 1995

Anderson SD. Specific problems: Exercise-induced asthma (Chapter 34). In: O'Byrne PO, Thompson NC editor(s). *Manual of Asthma Management*. London: WB Sanders Company Ltd, 1995:621–43.

Anderson 2000

Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is.... *Journal of Allergy & Clinical Immunology* 2000;**106**(3):453–59.

ATS 1993

American Thoracic Society. Guidelines for the evaluation of impairment/disability in patients with asthma. *American Review of Respiratory Disease* 1993;**147**:1056–61.

Beck 1997

Beck KC. Evaluating exercise capacity and airway function in the athlete (Chapter 2). In: Weiler JM editor(s). *Allergic and Respiratory Disease in Sports Medicine*. New York: Marcel Dekker, Inc, 1997:35–64.

Boner 1988

Boner AL, Vallone G, Peroni DG, Piacentini GL, Gaburro D. Efficacy and duration of action of placebo responses in the prevention of exercise-induced asthma in children. *Journal of Asthma* 1988;**25**(1):1–5.

Brudno 1994

Brudno DS, Wagner JM, Rupp NT. Length of postexercise assessment in the determination of exercise-induced bronchospasm. *Annals of Allergy* 1994;**73**(3):227–31.

CC Handbook

Mulrow CD, Oxman AD (editors). Analysing and presenting results. Cochrane Reviewers' Handbook [updated March 1997]; Section 8. In: The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration. Oxford: Update Software 1997.

Chhabra 1998

Chhabra SK, Ojha UC. Late asthmatic response in exercise-induced asthma. *Annals of Allergy Asthma & Immunology* 1998;**80**(4):323–7.

Eggleston 1984

Eggleston PA. Methods of exercise challenge. *Journal of Allergy & Clinical Immunology* 1984;**73**:666–9.

Ernst 1996

Ernst P, Fitzgerald JM, Spier S. Canadian Asthma consensus Conference: Summary of recommendations. *Canadian Respiratory Journal* 1996;**3**(2):89–100.

ERS Task Force 1997

ERS Task Force. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. *European Respiratory Journal* 1997; **10**:2662–89.

Godfrey 1987

Godfrey S, Bar-Yishay E. Exercise-induced asthma revisited. *Respiratory Medicine* 1993;**87**:331–44.

Gotshall 2002

Gotshall R. Exercise-induced bronchoconstriction. *Drugs* 2002;**62**(12):1725–39.

Hogshead 1989

Hogshead N, Couzens GS. *Asthma and Exercise*. New York: Henry Holt and Company, 1989.

Jadad 1996

Jadad AR, Moore RA, Carrol D, et al.Assessing the quality of reports of randomized clinical trials: Is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1–12.

Kelly 2000

Kelly K, Spooner CH, Rowe BH. Nedocromil sodium versus sodium cromoglycate for preventing exercise-induced bronchoconstriction in asthmatics. *The Cochrane Database*

of Systematic Reviews 2000, Issue 3. [Art. No.: CD002731. DOI: 10.1002/14651858.CD002731]

Kuzemo 1989

Kuzemo JA. Twenty years of sodium cromoglycate treatment: a short review. *Respiratory Medicine* 1989;**83** (Suppl):11–16.

Massie 2002

Massie J. Exercise-induced asthma in children. *Paediatric Drugs* 2002;**4**(4):267–78.

McCarthy 1989

McCarthy P. Wheezing and breezing through exercise-induced asthma. *Physician and Sports medicine* 1989;**17**(7): 125–30.

Mehta & Busse 1997

Mehta H, Busse WW. Prevalence of exercise-induced asthma in the athlete. (Chapter 4). In: Weiler JM editor (s). *Allergic and Respiratory Disease in Sports Medicine*. New York: Marcel Dekker, Inc, 1997.

Nemet 2000

Nemet D, Wolach B, Yacobovich J, Eliakim A. Exercise in childhood asthma: provoking agent, diagnostic tool and therapeutic measure. *Israel Medical Association Journal* 2000;**2**(2):99–103.

Pierson 1988

Pierson WE, Voy RO. Exercise-induced bronchospasm in the XXIII summer Olympic games. *New England and Regional Allergy Proceedings* 1988;**9**(3):209–13.

Randolph 1997

Randolph C. Exercise-induced asthma:Update on pathophysiology, clinical diagnosis, and treatment. *Current Problems in Pediatrics* 1997;**27**:53–77.

Rundell 2002

Rundell K, Jenkinson D. Exercise-induced bronchospasm in the elite athlete. *Sports Medicine* 2002;**32**(9):583–600.

Rupp 1996

Rupp NT. Diagnosis and management of exercise-induced asthma. *Physician and Sportsmedicine* 1996;**24**(1):77–87.

Santanello 1999

Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial?. *European Respiratory Journal* 1999;**14**: 23–7.

Senn 1991

Senn S, Hildebrand H. Crossover trials, degrees of freedom, the carryover problem and its dual. *Statistics in Medicine* 1991;**10**:1361–74.

Sly 1984

Sly RM. Beta-adrenergic drugs in the management of asthma in athletes. *Journal of Allergy & Clinical Immunology* 1984;**73**:680–5.

Spector 1993

Spector SL. Update on exercise-induced asthma. *Annals of Allergy* 1993;**71**:571–7.

Spooner 1998

Spooner CH, Saunders LD, Rowe BH. Nedocromil sodium for preventing exercise-induced bronchoconstriction. *The Cochrane Database of Systematic Reviews* 2002, Issue 1. [Art. No.: CD001183. DOI: 10.1002/14651858.CD001183]

Virant 1992

Virant FS. Exercise-induced bronchospasm: epidemiology, pathophysiology, and therapy. *Medicine and Science in Sports & Exercise* 1992;**24**:851–5.

Weiler 1996

Weiler JM. Exercise-induced asthma: a practical guide to definitions, diagnosis, prevalence, and treatment. *Allergy and Asthma Proceedings* 1996;**17**(6):315–25.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Boner 1987

Methods	Methods: RCT, DB, X-over Withdrawals: 0 Def'n EIB: Fall FEV1=>20% Exercise challenge: inclined treadmill x 6 min, 90% predicted maximum HR. 4 challenges in 4 consecutive days, same time of day.
Participants	Country: Italy Recruitment: Volunteers from home for asthmatics Sample size: 15; M =10, F=5. Mean age: 11.7y sd 14 Inclusion: Hx of asthma and EIB, all allergic, no CS in past 2 mo., all > 80% predicted normal. Exclusion: hypotension, sick sinus syndrome, AV-block, Mean severity on placebo: max fall FEV1=40.9% sd 17.2
Interventions	Delivery method: nebuliser Time administered pre-challenge: 30 min Mast cell agent/dose: SCG 20mg Anticholinergic/dose: IB 500ug Concomitant meds stopped: BDs x 12 hr., others 24h - 1 wk.
Outcomes	Reported outcomes: FEV1: maximum % fall Complete protection Clinical protection ADRs: none were seen Excluded: Verapamil results
Notes	Jadad score: 3 Statistical issues: results calculated from IPD

Risk of bias

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

Boulet 1889

Methods	Methods: RCT, DB, X-over Withdrawals: 1 withdrawal (exacerbation) Def'n EIB: Fall FEV1 >10% Exercise challenge: inclined treadmill x 6 min, 90% predicted maximum HR. 11 challenges in 6 wks. q2 days, same time of day.
Participants	Country: Canada Recruitment: volunteers Sample size: 11; M=4, F=7. Mean age: 30y sd 10.9 Inclusion: Hx asthma (ATS criteria) & EIB, none on OCS, 4/11 on ICS > 65% predicted, all used B2 prn, 5 on theophylline. Exclusion: CV disease, unstable asthma, URTI. Mean severity on placebo: NR
Interventions	Delivery method: MDI/spacer Time administered pre-challenge: 30 min Mast cell agent/dose: SCG 4 mg Beta2 agonist/dose: salbutamol 200ug Anticholinergic/dose: IB 80 ug Concomitant meds stopped: 8-24 hrs
Outcomes	Reported outcomes: Clinical protection ADRs: NR
Notes	Jadad score: 4 Statistical issues: none

Risk of bias

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

Bundgaard 1980

Methods	Methods: RCT, DB, X-over Withdrawals: 0 Def'n EIB: Fall FEV1>20% Exercise challenge: 3 periods free running 2min + 1min rest, HR>160. 5 challenges on 5 consecutive days, same time of day.
Participants	Country: Denmark Recruitment: Asthma clinic Sample size: 18; M=7, F=11. Mean age: 30.5y sd 7.6 Inclusion: Hx asthma, 17/18 had allergies, normal heart function and chest Xrays, 3/18 were smokers, none on OCS.

Bundgaard 1980 (*Continued*)

	Exclusion: NR Mean severity on placebo: Max fall PEFR 33.5%
Interventions	Delivery method: nebuliser Time administered pre-challenge: 30-45 min Mast cell agent/dose: SCG 20 mg Beta2 agonist/dose: fenoterol 2 mg Anticholinergic/dose: IB 0.5 mg Combined SCG/IB 20mg/0.5 mg Concomitant meds stopped: x 24 hr
Outcomes	Reported outcomes: PEFR: maximum % fall PEFR based on top-bottom index . ADRs: tremor, 'distress' Excluded: combination SCG/IB results and oral medication results
Notes	Jadad score: 3 Statistical issues: Values estimated from graphs. Error bars = 2 SEM

Risk of bias

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

Bundgaard 1983a

Methods	Methods: RCT,(table of random numbers) DB, X-over, double-dummy Withdrawals: 0 Def'n EIB: Fall PEFR =>20% Exercise challenge: inclined treadmill x 6 min. HR > 160. 4 challenges in 7 days. Same time of day. T=23C, RH=45%
Participants	Country: Denmark Recruitment: N/R Sample size: 15; M/F NR . Mean age: 33y (21-46) Inclusion: Hx Asthma, lung function >50% predicted. All used B2 agonists prn. None on systemic CS. Exclusion: N/R Mean severity on placebo: Max fall PEFR 33.0% sd 15.49
Interventions	Delivery method: spinhaler Time administered pre-challenge: 30 min Mast cell agent/dose: SCG 20 mg Beta2 agonist/dose: fenoterol 0.4 mg Combintion SCG/fen 20mg/0.4 mg Concomitant meds stopped: B2 x 8 hr, others x 24 hr

Bundgaard 1983a (*Continued*)

Outcomes	Reported outcomes: PEFR: mean% fall PEFR based on top-bottom index . ADRs. None were observed
Notes	Jadad score: 4 Statistical issues: Data from text.

Risk of bias

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

Bundgaard 1983p

Methods	Methods: RCT, DB, X-over, double-dummy Withdrawals: 0 Def'n EIB: Fall PEFR =>20% Exercise challenge: inclined treadmill x 6 min. HR > 160. 4 challenges in 7 days. Same time of day. T=23C, RH=45%
Participants	Country: Denmark Recruitment: volunteers from clinic Sample size: 17; M= 7, F= 10. Mean age: 12y (range 9-14) Inclusion: Hx Asthma, stable asthma, reproducible EIB. All used B2 agonists. None on CS. Exclusion: N/R Mean severity on placebo: Max fall PEFR =27.0% sd 8.25
Interventions	Delivery method: spinhaler Time administered pre-challenge: 30 min Mast cell agent/dose: SCG 20 mg Beta2 agonist/dose: fenoterol 0.4 mg Combintion SCG/fen 20mg/0.4 mg Concomitant meds stopped: B2 x 8 hr, others x 24 hr.
Outcomes	Reported outcomes: PEFR: mean% fall PEFR based on top-bottom index . ADRs. None were observed
Notes	Jadad score: 4 Statistical issues: Data from text.

Risk of bias

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

Bundgaard 1986neb

Methods	Methods: RCT (4x4 William's Square), DB, X-over (conducted 2 studies same protocol, different participants) Withdrawals: 0 Def'n EIB: N/R but mean fall PFT 30% on placebo Exercise challenge: inclined treadmill x 6 min consistent settings, 8 challenges 8 days T=23C, RH=50%
Participants	Country: Denmark Recruitment: N/R Sample size: 16 children; M/F N/R Mean age: N/R Inclusion: lung function>50% predicted, none on OCS, 4/6 on ICS. Exclusion: Mean severity on placebo: max fall PEFR 31.0% sd 16.6
Interventions	Delivery method: nebulizer Time administered pre-challenge: 10 min Mast cell agent/dose: SCG 20mg Beta2 agonist/dose: 2.5mg Combined SCG/B2 20mg/2.5 mg Concomitant meds stopped: oral meds x 24 hrs. inhaled meds x 8 hr
Outcomes	Reported outcomes: PEFR: maximum % fall based on top-bottom index ADRs: N/R
Notes	Jadad score: 4 Statistical issues: sd estimated from SEM bars on graphs

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	4x4 William's Square, DB, X-over, conducted 2 studies same protocol, different participants

Bundgaard 1986pdr

Methods	Methods: RCT (4x4 William's Square), DB, X-over (same protocol as Bundgaard 86n, independent participants) Withdrawals: 0 Def'n EIB: N/R but mean fall PFT 30% on placebo Exercise challenge: inclined treadmill x 6 min consistent settings, 8 challenges in 8 days. T=23C, RH=50%
Participants	Country: Denmark Recruitment: N/R Sample size: 16 children; M/F N/R Mean age: N/R

Bundgaard 1986pdr (*Continued*)

	Inclusion: lung function>50% predicted, none on OCS, 4/16 on ICS. Exclusion: N/R Mean severity on placebo: max fall PEFR 30% sd 11.43
Interventions	Delivery method: spinhaler Time administered pre-challenge: 10 min Mast cell agent/dose: SCG 20mg capsule Beta2 agonist/dose: salbutamol 0.4 mg capsule Combined SCG/B2: 20mg/0.4 mg Concomitant meds stopped: oral meds x 24 hrs. inhaled meds x 8 hr
Outcomes	Reported outcomes: PEFR: maximum % fall based on top-bottom index ADRs: N/R
Notes	Jadad score: 4 Statistical issues: sd estimated from SEM bars on graphs

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	4x4 William's Square, DB, X-over, conducted 2 studies same protocol, different participants

Clarke 1990

Methods	Methods: RCT (Latin Square), DB, double dummy, X-over Withdrawals: 0 Def'n EIB: max fall FEV1 =>15% Exercise challenge: inclined treadmill x 6 min consistent settings, HR=150. 8 challenges over 2 wks.
Participants	Country: Australia Recruitment: voluneers from clinic Sample size: 20: M=14, F=6. Mean age: 29.4y Inclusion: Hx asthma, steroid use not reported Exclusion: N/R Mean severity on placebo: max fall FEV1 15%
Interventions	Delivery method: Spinhaler/MDI double dummy Time administered pre-challenge: 10 min Mast cell agent/dose: SCG 20 mg Beta2 agonist/dose: fenoterol 100ug Concomitant meds stopped: x 2 days

Clarke 1990 (*Continued*)

Outcomes	Reported outcomes: FEV1: maximum % fall Complete protection Clinical protection ADRs: none were seen
Notes	Jadad score: 5 Statistical issues: SDs imputed from weighted average of other included studies

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Latin Square, DB, double dummy, X-over.

de Benedictis 1998

Methods	Methods: RCT, DB, Double dummy, X-over Withdrawals: 0 Def'n EIB: Max fall FEV1=>15% Exercise challenge: inclined treadmill x 6 min. HR=85% of max predicted, consistent settings, 3 challenges in 10 days, same time of day. T=23C, RH=44-57%
Participants	Country: Italy Recruitment: volunteers from asthma clinic Sample size: 12; M=9, F=3. Mean age: 10.0 y sd 2.0 Inclusion: Hx asthma (ATS criteria), all on treatment with various anti-asthma drugs, some on ICS. >70% predicted, BL values >80% predicted. Exclusion: URTI within 4 wks, variability >10% between tests Mean severity on placebo: max fall FEV1 31.0% sd 14.1
Interventions	Delivery method: MDI Time administered pre-challenge: 20 min Combination Mast cell agent/dose: NCS 4 mg/Salbutamol 200ug Beta2 agonist/dose: salbutamol 200ug Concomitant meds stopped: x 12 hrs.
Outcomes	Reported outcomes: FEV1: maximum % fall FEV1 Complete protection Clinical protection ADRs: none were seen
Notes	Jadad score: 4 Statistical issues: IPD reported and used to calculate clinical protection. Patient 5 deleted as no EIB on placebo.

de Benedictis 1998 (*Continued*)

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

Debelic 1988

Methods	Methods: RCT, DB, X-over Withdrawals: 0 Def'n EIB: Max fall FEV1 =>20% Exercise challenge: free running x 6 min. same time of day. HR 160-180. 4 challenges in 4 test days. T=18-20C,
Participants	Country: Germany Recruitment: N/R Sample size: 16; M/F: N/R Mean age: 13.8 (8-20yrs) Inclusion: Hx asthma, all allergic, reproducible EIB, PFT =>70% predicted. None on CS. Exclusion: N/R Mean severity on placebo: max fall FEV1 43%
Interventions	Delivery method: MDI Time administered pre-challenge: 15 min Mast cell agent/dose: SCG 2mg Beta2 agonist/dose: reproterol 1mg Combination SCG/reproterol 2mg/1mg Concomitant meds stopped: x 12 hr
Outcomes	Reported outcomes: FEV1: maximum % fall Complete protection Clinical protection ADRs: none were observed
Notes	Jadad score: 3 Statistical issues: Values calculated from IPD. Patient 13, 14 omitted-no EIB on placebo

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

Dorward 1982

Methods	Methods: RCT, SB, double-dummy, X-over Withdrawals: 0 Def'n EIB: max fall FEV1=>25% Exercise challenge: inclined treadmill x8 min, consistent settings, HR 170-180. T=20-22C, RH=30-50%
Participants	Country: UK Recruitment: volunteers Sample size: 7; M=2, F=5 Mean age: 24y sd 18.39 Inclusion: Hx allergic asthma, all were non-smokers. Exclusion: OCS or ICS users Mean severity on placebo: max fall FEV1 47% sd 6.95
Interventions	Delivery method: nebulizer Time administered pre-challenge: 1 hr Mast cell agent/dose: SCG 12 mg Anticholinergic/dose: IB 120ug Concomitant meds stopped: x 24 hrs. All received ketotifen 2.0 mg or placebo 90 min before test drugs
Outcomes	Reported outcomes: FEV1: maximum % fall Complete protection Clinical protection ADRs: N/R Results for clemastine and ketotifen not included.
Notes	Jadad score: 2 Statistical issues: Values calculated from IPD table 3 All received ketotifen 90 minutes prior to other drugs. Since it had no effect on EIB included the study

Risk of bias

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

Gehrke 1986

Methods	Methods: RCT, DB, X-over Withdrawals: 2 Def'n EIB: max fall PFT =>20% Exercise challenge: treadmill x 6 min. 5 challenges over 5 different days
Participants	Country: Germany Recruitment: N/R Sample size: 10; M=6, F=4. Mean age: 19-48 yrs Inclusion: Hx EIB, PFT >65%, steroid use not reported. Exclusion: N/R

Gehrke 1986 (*Continued*)

	Mean severity on placebo: Max fall PEFR 46.1% sd 11.7%
Interventions	Delivery method: NR Time administered pre-challenge: 15 min Mast cell agent/dose: SCG 1 mg Beta2 agonist/dose: fenoterol 0.05 mg and 0.2 mg Combined SCG/fenoterol 1 mg/0.05 mg Concomitant meds stopped: oral x24h, inhaled x 8 hr.
Outcomes	Reported outcomes: PEFR: maximum % fall ADRs: tremor/agitation
Notes	Jadad score: 3 Statistical issues: results calculated from IPD, dropouts not included

Risk of bias

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

Godfrey 1975

Methods	Methods: RCT, SB, X-over Withdrawals: 0 Def'n EIB: NR but max fall PEFR=44.87% sd 15.6 on placebo. Exercise challenge: inclined treadmill x 6 min, Hr =170-180, consistent settings, 4 challenges over 4 days in 2 separate 1 wk periods.
Participants	Country: UK Recruitment: Volunteers, Dept. Pediatrics Sample size: 15; M=13, F=2. Mean age: 8.7 yr Inclusion: Hx asthma, PFT >65% predicted, steroid use not reported. Exclusion: N/R Mean severity on placebo: Max fall PEFR 45.2% sd 15.49%
Interventions	Delivery method: MDI, spinhaler, oral, nebuliser. Time administered pre-challenge: 10 min inhaled, 2 hrs oral Mast cell agent/dose: SCG 20 mg spinhaler Beta2 agonist/dose: salbutamol 200ug MDI (13 pts) oral 3-4 mg (2 pts) Anticholinergic agent/dose: Atropine 0.2% sol'n @ 9 L/min x 3 min IV Concomitant meds stopped: x 12 hr.
Outcomes	Reported outcomes: PEFR: maximum % fall Complete protection

Godfrey 1975 (*Continued*)

	Clinical protection ADRs: N/R Theophylline results not included
Notes	Jadad score: 2 Statistical issues: results estimated from IPD Table 2. Authors saw no difference between delivery methods so combined results

Risk of bias

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

Godfrey 1976

Methods	Same study as Godfrey 1975
Participants	Same study as Godfrey 1975
Interventions	Same study as Godfrey 1975
Outcomes	Same study as Godfrey 1975
Notes	Same study as Godfrey 1975

Risk of bias

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

Neijens 1981a

Methods	Methods: RCT, DB, X-over Withdrawals: 0 Def'n EIB: max fall FEV1 >15% Exercise challenge: inclined treadmill x 6 min. HR 175, consistent settings, 4 challenges in 4 consecutive days. T=22C, RH=70%
Participants	Country: Netherlands Recruitment: Volunteers from Outpatient clinic Sample size: 13; M=9, F=4. Mean age: 12.5 yrs Inclusion: Hx asthma, PFT >60% predicted, stable, reproducible EIB Exclusion: If receiving SCG, CS, B2 agonists in past 2 wks. Mean severity on placebo: max fall FEV1 27.5% sd 11.54%

Neijens 1981a (*Continued*)

Interventions	Delivery method: MDI, nebuliser. Time administered pre-challenge: 20 min Mast cell agent/dose: SCG 20mg Beta2 agonist/dose: fenoterol 0.4 mg Anticholinergic/dose: oxytropium bromide 0.02 mg Concomitant meds stopped: x 3 days
Outcomes	Reported outcomes: FEV1: maximum % fall ADRs: N/R
Notes	Jadad score: 2

Risk of bias

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

Obata 1993

Methods	Methods: RCT, DB, X-over Withdrawals: 0 Def'n EIB: max fall PEFR >20% Exercise challenge: bicycle x 6 min, consistent settings, 3 challenges on 3 separate days over 10 days. T=20-24C, RH=56-67%
Participants	Country: Japan Recruitment: N/R Sample size: 14; M=10, F=4. Mean age: 12.7y sd 3.0 Inclusion: Hx asthma (ATS criteria), PFT >70% predicted. None on OCS, 6/14 on ICS Exclusion: N/R Mean severity on placebo: Max fall PEFR 39.6% sd 16.09%
Interventions	Delivery method: nebulizer Time administered pre-challenge: 1 hr Mast cell agent/dose: SCG 20mg Beta2 agonist/dose: procaterol 1ug/kg Concomitant meds stopped: theophylline x 24 hr, others x 12 hr
Outcomes	Reported outcomes: PEFR: maximum % fall Complete protection Clinical protection ADRs: N/R

Obata 1993 (*Continued*)

Notes	Jadad score: 3 Statistical issues: Results calculated from IPD

Risk of bias

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

Pichaipat 1995

Methods	Methods: no blinding, X-over Withdrawals: 3 (no EIB on test run) Def'n EIB: Max fall FEV1=>20% Exercise challenge: bicycle x 7-8 min. HR>170, consistent settings, 4 challenges over 45 days, 7 days between. T=23-25C, RH=65-75%
Participants	Country: Thailand Recruitment: Pediatric allergy clinic Sample size: 11; M=8, F=3. Mean age: 11y Inclusion: Hx asthma & EIB. None on CS, antihistamine or anticholinergics. PFT >80% predicted on test day. None on OCS or ICS. Exclusion: No heart disease, URTI, active bronchospasm or thyrotoxicosis. Mean severity on placebo: max fall FEV1 28.23% sd 7.98%
Interventions	Delivery method: MDI Time administered pre-challenge: 15 min Mast cell agent/dose: SCG 10 mg Beta2 agonist/dose: terbutaline 200 ug Concomitant meds stopped: Methylxanthine and B2 x 8 -12 hrs, SCG and CS x 24 hr
Outcomes	Reported outcomes: FEV1: maximum % fall Complete protection Clinical protection ADRs: N/R Budesonide results not included.
Notes	Jadad score: 1 Statistical issues: results calculated from IPD It is not known if study was randomized but is included pending contact with the author

Risk of bias

Item	Authors' judgement	Description

Pichaipat 1995 (*Continued*)

Allocation concealment?	Unclear	Information not available

Rohr 1987

Methods	Methods: RCT, SB (evaluator), parallel group Withdrawals: 3 Def'n EIB: Max fall FEV1=>20% Exercise challenge: inclined treadmill x 6-8 min HR 80-90% max. consistent settings, 2 challenges 1 week apart. T=25C, RH=47%
Participants	Country: USA, 2 centres Recruitment: N/R Sample size: 80; M=46, F=37. Mean age: 24y Inclusion: Hx asthma (mild), Hx EIB, none on CS. Exclusion: N/R Mean severity on placebo: max fall FEV1 32%
Interventions	Delivery method: spinhaler, MDI Time administered pre-challenge: 15 min Mast cell agent/dose: SCG 20 mg Beta2 agonist/dose: albuterol 180 ug Concomitant meds: none permitted throughout the study
Outcomes	Reported outcomes: FEV1: maximum % fall Complete protection ADRs: N/R
Notes	Jadad score: 1 Statistical issues: sd imputed from weighted average of other studies

Risk of bias

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

Spada 1985

Methods	Methods: RCT, crossover Withdrawals: 0 Def'n EIB: Max fall FEV1 =>15% Exercise challenge: treadmill at 80% maximum cardio function 4 challenges. T=18-22 C, RH 40-50%,
Participants	Country: Italy Recruitment: ambulatory volunteers Sample size: 100; M=65, F=35. Mean age: 19.8y sd 10.2 Inclusion: Hx asthma (ATS criteria), reproducible EIB, at 80% of predicted PFT, steroid use not reported. Exclusion: Mean severity on placebo: max fall FEV1 22.82% sd 5.29%
Interventions	Delivery method: MDI Time administered pre-challenge: 15-45 min. Mast cell agent/dose: SCG 20 mg Beta2 agonist/dose: salbutamol 0.2 mg Anticholinergic/dose: IB 40 ug Concomitant meds stopped: x 24 hr
Outcomes	Reported outcomes: FEV1: change in % predicted Complete protection ADRs: N/R
Notes	Jadad score: 2

Risk of bias

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

Svenonius 1988

Methods	Methods: RCT, SB (patient), X-over Withdrawals: 0 Def'n EIB: Max fall FEV1 =>20% Exercise challenge: inclined treadmill x 6 min. HR 170. Consistent settings, 5 challenges.
Participants	Country: Sweden Recruitment: volunteers Sample size: 7; M=3, F=3. Mean age: 13.9y sd 2.9 Inclusion: Hx asthma, Reproducible EIB, only on SABA, none on CS. Exclusion: if had infection or asthma exacerbation Mean severity on placebo: max fall FEV1 22.82% sd 5.29%

Svenonius 1988 (*Continued*)

Interventions	Delivery method: MDI & spacer Time administered pre-challenge: 15 min. IB 1 hr. Mast cell agent/dose: SCG 3 mg Beta2 agonist/dose: salbutamol 0.3 mg Anticholinergic/dose: IB 80 ug Combined SCG/B2 Concomitant meds stopped: x 12 hr (only on B2 agonists)
Outcomes	Reported outcomes: FEV1: change in % predicted Complete protection ADRs: N/R
Notes	Jadad score: 2 Statistical issues: % predicted results not included.

Risk of bias

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

Thompson 1978

Methods	Methods: RCT, DB, X-over Withdrawals: 0 Def'n EIB: N/R Exercise challenge: inclined treadmill x 5-8 min. HR 170-180. Consistent settings. 4 challenges in 10 days.
Participants	Country: UK Recruitment: N/R Sample size: 13; M=7, F=6. Mean age: (17-33y) Inclusion: Hx asthma, all non-smokers. Exclusion: current ICS use Mean severity on placebo: Max fall FEV1 38%
Interventions	Delivery method: nebulizer Time administered pre-challenge: 20 min Mast cell agent/dose: SCG 20 mg Anticholinergic/dose: IB 2.0 mg Combined SCG/IB Concomitant meds stopped: x 24 hr

Thompson 1978 (*Continued*)

Outcomes	Reported outcomes: FEV1: maximum % fall ADRs: none were seen Combination results not included.
Notes	Jadad score: 3 Statistical issues: reviewers averaged the results from helium responder/nonresponder groups weighted by sample size

Risk of bias

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

Tullett 1982

Methods	Methods: RCT, SB, X-over Withdrawals: 4 (severe bronchoconstriction after inhaling lignocaine) Def'n EIB: =>20% Exercise challenge: inclined treadmill x 8 min. HR 160. Consistent settings, 4 challenges in 7-10 days. T=20-22C, RH=20-40%
Participants	Country: UK Recruitment: N/R Sample size: 8; M=5, F=3. Mean age: 31.2y sd 11.31 Inclusion: Hx asthma, reproducible EIA. All non-smokers. Exclusion: Current OCS/ICS or antihistamine use Mean severity on placebo: Max fall FEV1 37.28% sd12.55%
Interventions	Delivery method: nebulizer Time administered pre-challenge: 30 min Mast cell agent/dose: SCG 12 mg Anticholinergic/dose: IB 120ug Concomitant meds stopped: x 24 hr.
Outcomes	Reported outcomes: FEV1: maximum % fall Complete protection Clinical protection ADRs: both well tolerated Lignocaine results not included
Notes	Jadad score: 2 Statistical issues: results calculated from IPD

Risk of bias

Tullett 1982 (*Continued*)

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

Vazquez 1984

Methods	Methods: RCT, DB, parallel Withdrawals: 0 Def'n EIB: max fall FEV1 =>15% Exercise challenge: stair climbing as fast as possible for 5-8 min. HR = 170 T/RH - NR
Participants	Country: Spain Recruitment: volunteers from clinic Sample size: 49; M/F NR. Mean age: 9.4y sd 2.05 Inclusion: Hx of EIB. All except 2 were atopic. Asymptomatic asthma (ATS criteria), 80 of predicted, steroid use not reported. Exclusion: NR Mean severity on placebo: Max fall FEV1 14.3% sd9.8
Interventions	Delivery method: nebulised Time administered pre-challenge: 15 min Mast cell agent/dose: SCG 20 mg N=12 Beta2 agonist/dose: salbutamol 4mg N=13 Anticholinergic: IB 0.4mg N=12 Placebo: N=12 Concomitant meds stopped:
Outcomes	Reported outcomes: FEV1: Complete protection ADRs:
Notes	Jadad score: 3 Statistical issues: original paper in Spanish.

Risk of bias

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

Woolley 1990

Methods	Methods: RCT (Latin Square), DB, X-over Withdrawals: 0 Def'n EIB: max fall FEV1 =>20% Exercise challenge: inclined treadmill x 8 min. to 60% MVV consistent settings, 4 challenges separated by 2 hrs. on separate days over 3 wks. T=19-22C, RH=59-83%
Participants	Country: Australia Recruitment: volunteers Sample size: 12; M=7, F=5. Mean age: 20.9y sd 3.2 Inclusion: Hx of EIB needing treatment. All non-smokers. PFT >60% predicted on test days and stable over test period. 1/12 on ICS Exclusion: Mean severity on placebo: max fall FEV1 33.75%
Interventions	Delivery method: MDI Time administered pre-challenge: 10 min Mast cell agent/dose: SCG 2.0 mg Beta2 agonist/dose: terbutaline 0.5mg Combination SCG/terbutaline Concomitant meds stopped: inhaled x 8 hr, oral x 24 hr.
Outcomes	Reported outcomes: FEV1: maximum % fall Complete protection Clinical protection ADRs: mild throat irritation on SCG
Notes	Jadad score: 5 Statistical issues: none

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Third party, concealed randomisation

Zanconato 1990

Methods	Methods: RCT, X-over Withdrawals: 0 Def'n EIB: max fall FEV1 =>20% Exercise challenge: inclined treadmill @6.5 k/hr until exhaustion. Performed in afternoon. 3 challenges in 15 days. T=21-24C, RH= 50-70%.
Participants	Country: Italy Recruitment: Allergy centre in pediatric department Sample size: 12; M=8, F=4.

Zanconato 1990 (*Continued*)

	Mean age: 10.7y sd 2.8 Inclusion: all had mild to moderate atopic asthma. 3/12 on ICS. Exclusion: N/R Mean severity on placebo: max fall FEV1 32.8% sd 11.6%
Interventions	Delivery method: Spinhaler and MDI Time administered pre-challenge: 30 min. Mast cell agent/dose: SCG 40 mg (spinhaler) Beta2 agonist/dose: Albuterol 200ug MDI Concomitant meds stopped: x 24 hr.
Outcomes	Reported outcomes: FEV1: maximum % fall ADRs: N/R
Notes	Jadad score: 2 Statistical issues: none

Risk of bias

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

ADR=adverse reaction
B2=beta 2 agonist
BD=bronchodilators
BL=baseline
CS=corticosteroids OCS=oral corticosteroids ICS=inhaled corticosteroids
CV=cardiovascular disease
DB=double blind SB=single blind
Def'n=definition of EIB used
EIB=exercise-induced bronchospasm
F=female
FEV1=forced expiratory volume in one second
HR=heart rate
Hx=history of
IB=ipratropium bromide
IPD= Individual patient data
M=male
MDI=metered dose inhaler
neb=nebulizer
NR=not reported
PEFR=peak expiratory flow rate
PFT = pulmonary function test
RCT=randomised controlled trial
RH=relative humidity
SCG=sodium cromoglycate

SDs=standard deviations
URTI=upper respiratory tract infection
Complete protection = <15% fall in PFT post exercise

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

Study	Reason for exclusion
Bauer 1979	No included outcome measures
Bauer 1981	No included outcome measures
Boner 1984	Not an RCT (author communication)
Bundgaard 1983	Not right interventions
Ceugniet 1997	Not right interventions
Cummings 1984	Not randomized, drugs given sequentially
De Cree 1980	Not right interventions
Eggleston 1972	Placebo control
Gimeno 1985	Patients had COPD
Guerin 1992	Not right interventions
Johnson 1986	No included outcome measures Reported change from 0, no baseline values reported
Joppich 1987	Not randomised
Neijens 1981b	CARA is not asthma
Rachelefsky 1978	No included outcome measures
Rasmussen 1979	Only reported the Jones liability index
Ringel 1982	Not right interventions
Spada 1984	Abstract only
Tabas 1985	Beta agonists were given orally. Not stated if randomized.
Tashkin 1977	No included outcome measures

(*Continued*)

Verini 1983	Not an RCT
Woolley 1988	Abstract only

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

DATA AND ANALYSES

Comparison 1. MCS vs anticholinergics (AC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum percent decrease in PFT	8	358	Mean Difference (IV, Random, 95% CI)	-6.68 [-10.04, -3.31]
1.1 Children	4	102	Mean Difference (IV, Random, 95% CI)	-6.56 [-12.17, -0.95]
1.2 Adults	4	256	Mean Difference (IV, Random, 95% CI)	-6.74 [-10.95, -2.54]
2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved)	8	346	Odds Ratio (M-H, Random, 95% CI)	2.15 [1.26, 3.68]
2.1 Children	4	90	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.39, 6.16]
2.2 Adults	4	256	Odds Ratio (M-H, Random, 95% CI)	2.55 [1.46, 4.44]
3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved)	5	104	Odds Ratio (M-H, Random, 95% CI)	2.70 [1.14, 6.41]
3.1 Children	2	52	Odds Ratio (M-H, Random, 95% CI)	3.31 [0.92, 11.86]
3.2 Adults	3	52	Odds Ratio (M-H, Random, 95% CI)	2.28 [0.70, 7.36]
4 Mean degree of clinical protection: PFT comparison	6	130	Mean Difference (IV, Random, 95% CI)	11.21 [2.40, 20.02]
4.1 Children	3	78	Mean Difference (IV, Random, 95% CI)	10.73 [1.25, 20.21]
4.2 Adults	3	52	Mean Difference (IV, Random, 95% CI)	14.05 [-17.70, 45.79]
5 ADRS	4	108	Odds Ratio (M-H, Random, 95% CI)	Not estimable
5.1 General side effects	4	108	Odds Ratio (M-H, Random, 95% CI)	Not estimable
6 High vs low quality	8	358	Mean Difference (IV, Random, 95% CI)	-6.68 [-10.04, -3.31]
6.1 Low quality (Jadad 1-2)	4	252	Mean Difference (IV, Random, 95% CI)	-6.29 [-10.54, -2.04]
6.2 High quality (Jadad 3-5)	4	106	Mean Difference (IV, Random, 95% CI)	-7.32 [-12.82, -1.82]
7 Effect by severity	8	358	Mean Difference (IV, Random, 95% CI)	-6.68 [-10.04, -3.31]
7.1 Mild EIB (< 30% maximum fall on placebo)	3	250	Mean Difference (IV, Random, 95% CI)	-5.88 [-9.75, -2.00]
7.2 Severe EIB (=>30% maximum fall on placebo)	5	108	Mean Difference (IV, Random, 95% CI)	-9.12 [-15.90, -2.33]
8 Effect by steroid use	5	112	Mean Difference (IV, Random, 95% CI)	-8.36 [-14.26, -2.46]
8.1 No recent steroid use	5	112	Mean Difference (IV, Random, 95% CI)	-8.36 [-14.26, -2.46]
8.2 Some on ICS (no studies)	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

Comparison 2. MCS vs short acting beta-agonist (SABA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum percent decrease in PFT	12	543	Mean Difference (IV, Random, 95% CI)	6.84 [4.47, 9.22]
1.1 Children	7	183	Mean Difference (IV, Random, 95% CI)	7.30 [3.88, 10.73]
1.2 Adults	5	360	Mean Difference (IV, Random, 95% CI)	6.39 [2.67, 10.12]
2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved)	9	451	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.18, 0.52]
2.1 Children	6	147	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.07, 0.46]
2.2 Adults	3	304	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.75]
3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved)	6	154	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.18, 0.77]
3.1 Children	4	108	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.14, 0.88]
3.2 Adults	2	46	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.12, 1.34]
4 Mean degree of protection: PFT comparison	7	180	Mean Difference (IV, Random, 95% CI)	-22.67 [-33.42, -11.92]
4.1 Children	5	134	Mean Difference (IV, Random, 95% CI)	-21.55 [-34.15, -8.96]
4.2 Adults	2	46	Mean Difference (IV, Random, 95% CI)	-30.05 [-52.52, -7.57]
5 ADRS	10	304	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.00, 8.24]
5.1 General side effects	10	304	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.00, 8.24]
6 High vs low quality	12	543	Mean Difference (IV, Random, 95% CI)	7.06 [4.60, 9.52]
6.1 Low quality (Jadad 1-2)	5	356	Mean Difference (IV, Random, 95% CI)	7.51 [3.97, 11.04]
6.2 High quality (Jadad 3-5)	7	187	Mean Difference (IV, Random, 95% CI)	6.32 [2.47, 10.18]
7 Effect by severity	12	543	Mean Difference (IV, Random, 95% CI)	6.85 [4.45, 9.24]
7.1 Mild EIB (< 30% maximum fall on placebo)	4	273	Mean Difference (IV, Random, 95% CI)	4.06 [1.73, 6.39]
7.2 Severe EIB (=>30% maximum fall on placebo)	8	270	Mean Difference (IV, Random, 95% CI)	10.80 [7.44, 14.17]
8 By delivery method	12	401	Mean Difference (IV, Random, 95% CI)	11.12 [7.65, 14.59]
8.1 MDI	2	52	Mean Difference (IV, Random, 95% CI)	11.12 [-1.23, 23.48]
8.2 Spinhaler (Top/Bottom Index)	3	96	Mean Difference (IV, Random, 95% CI)	16.05 [11.95, 20.15]
8.3 Nebulisation	2	53	Mean Difference (IV, Random, 95% CI)	4.46 [-3.14, 12.06]
8.4 Two or more methods	5	200	Mean Difference (IV, Random, 95% CI)	9.94 [6.34, 13.55]
9 By Drug: MSC vs SABA	16	507	Mean Difference (IV, Random, 95% CI)	11.00 [7.76, 14.23]
9.1 Fenoterol	3	82	Mean Difference (IV, Random, 95% CI)	9.88 [3.26, 16.49]
9.2 Salbutamol	4	159	Mean Difference (IV, Random, 95% CI)	8.15 [2.71, 13.59]
9.3 Terbutaline	2	46	Mean Difference (IV, Random, 95% CI)	5.85 [2.11, 9.58]
9.4 Reproterol/procaterol	2	56	Mean Difference (IV, Random, 95% CI)	11.11 [1.57, 20.64]
9.5 Fenoterol (Top/Bottom Index)	3	100	Mean Difference (IV, Random, 95% CI)	17.60 [12.95, 22.24]
9.6 Salbutamol (Top/Bottom Index)	2	64	Mean Difference (IV, Random, 95% CI)	10.50 [-0.28, 21.28]

10 By method used to calculate change	16		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Percent Change Index	11	343	Mean Difference (IV, Random, 95% CI)	7.76 [5.23, 10.30]
10.2 Top-Bottom Index	5	164	Mean Difference (IV, Random, 95% CI)	14.71 [9.14, 20.29]
11 Effect by severity (TBI)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.3 Top/Bottom index (Severe EIB)	4	130	Mean Difference (IV, Random, 95% CI)	15.18 [8.07, 22.29]
12 Effect by steroid use	7	232	Mean Difference (IV, Random, 95% CI)	7.41 [4.73, 10.09]
12.1 No recent steroid use	4	156	Mean Difference (IV, Random, 95% CI)	6.35 [3.16, 9.53]
12.2 Some on ICS	3	76	Mean Difference (IV, Random, 95% CI)	10.00 [5.03, 14.96]

Comparison 3. SABA vs combination SABA + MCS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum percent decrease in PFT	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Children	2	50	Mean Difference (IV, Random, 95% CI)	1.83 [-1.25, 4.92]
1.2 Adults	3	80	Mean Difference (IV, Random, 95% CI)	1.31 [-6.29, 8.91]
2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved)	4	88	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.15, 1.39]
2.1 Children	3	64	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.09, 5.03]
2.2 Adults	1	24	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.07, 1.88]
3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved)	3	74	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.11, 1.21]
3.1 Children	2	50	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.52]
3.2 Adults	1	24	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.08, 2.66]
4 Mean degree of protection: PFT comparison	3	75	Mean Difference (IV, Random, 95% CI)	-10.26 [-26.99, 6.47]
4.1 Children	2	51	Mean Difference (IV, Random, 95% CI)	-10.26 [-26.99, 6.47]
4.2 Adults	1	24	Mean Difference (IV, Random, 95% CI)	Not estimable
5 ADRS	6	164	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.14, 7.10]
5.1 General side effects	6	164	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.14, 7.10]
6 Effect by severity	5	130	Mean Difference (IV, Random, 95% CI)	1.76 [-1.10, 4.62]
6.1 Mild EIB (< 30% maximum fall on placebo)	2	62	Mean Difference (IV, Random, 95% CI)	1.49 [-1.53, 4.51]
6.2 Severe EIB (=>30% maximum fall on placebo)	3	68	Mean Difference (IV, Random, 95% CI)	4.10 [-4.76, 12.97]
7 By method used to calculate change	9	258	Mean Difference (IV, Random, 95% CI)	0.42 [-0.81, 1.64]
7.1 Percent Change Index	5	130	Mean Difference (IV, Random, 95% CI)	1.76 [-1.10, 4.62]
7.2 Top/Bottom index	4	128	Mean Difference (IV, Random, 95% CI)	0.11 [-1.25, 1.47]

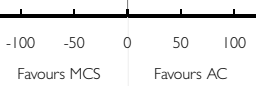
Analysis 1.1. Comparison 1 MCS vs anticholinergics (AC), Outcome 1 Maximum percent decrease in PFT.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 1 MCS vs anticholinergics (AC)

Outcome: 1 Maximum percent decrease in PFT

Study or subgroup	MCS N	MCS Mean(SD)	AC N	AC Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Children							
Boner 1987	15	15.5 (11.67)	15	21.73 (17.71)		9.8 %	-6.23 [-16.96, 4.50]
Godfrey 1976	15	19.33 (18.28)	7	24.57 (22.14)		3.2 %	-5.24 [-24.07, 13.59]
Neijens 1981a	13	6.7 (7.57)	13	12.5 (16.95)		11.1 %	-5.80 [-15.89, 4.29]
Vazquez 1984	12	4.2 (6.8)	12	12.1 (15.9)		11.8 %	-7.90 [-17.68, 1.88]
Subtotal (95% CI)	**55**		**47**			**36.0 %**	**-6.56 [-12.17, -0.95]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.12$, df = 3 (P = 0.99); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.29 (P = 0.022)							
2 Adults							
Dorward 1982	7	8.86 (11.88)	7	23.57 (19.79)		3.9 %	-14.71 [-31.81, 2.39]
Spada 1985	100	4.44 (16.2)	100	9.88 (17.31)		52.4 %	-5.44 [-10.09, -0.79]
Thompson 1978	13	14.58 (21.08)	13	26.39 (19.66)		4.6 %	-11.81 [-27.48, 3.86]
Tullett 1982	8	11.17 (11.48)	8	22.44 (25.07)		3.1 %	-11.27 [-30.38, 7.84]
Subtotal (95% CI)	**128**		**128**			**64.0 %**	**-6.74 [-10.95, -2.54]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.75$, df = 3 (P = 0.63); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.14 (P = 0.0017)							
Total (95% CI)	**183**		**175**			**100.0 %**	**-6.68 [-10.04, -3.31]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.87$, df = 7 (P = 0.97); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.89 (P = 0.00010)							



Analysis 1.2. Comparison 1 MCS vs anticholinergics (AC), Outcome 2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved).

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 1 MCS vs anticholinergics (AC)

Outcome: 2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved)

Study or subgroup	MCS n/N	AC n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Children					
Boner 1987	8/15	6/15		12.6 %	1.71 [0.40, 7.29]
Godfrey 1976	7/15	3/7		8.3 %	1.17 [0.19, 7.12]
Svenonius 1988	3/7	5/7		5.6 %	0.30 [0.03, 2.76]
Vazquez 1984	12/12	6/12		3.1 %	25.00 [1.21, 516.69]
Subtotal (95% CI)	**49**	**41**		**29.7 %**	**1.55 [0.39, 6.16]**
Total events: 30 (MCS), 20 (AC)					
Heterogeneity: Tau^2 = 0.90; Chi^2 = 5.61, df = 3 (P = 0.13); I^2 =47%					
Test for overall effect: Z = 0.62 (P = 0.53)					
2 Adults					
Dorward 1982	6/7	3/7		4.2 %	8.00 [0.60, 106.94]
Spada 1985	81/100	62/100		48.2 %	2.61 [1.37, 4.97]
Thompson 1978	7/13	5/13		11.0 %	1.87 [0.39, 8.89]
Tullett 1982	5/8	4/8		6.9 %	1.67 [0.23, 12.22]
Subtotal (95% CI)	**128**	**128**		**70.3 %**	**2.55 [1.46, 4.44]**
Total events: 99 (MCS), 74 (AC)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.08, df = 3 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 3.29 (P = 0.00099)					
Total (95% CI)	**177**	**169**		**100.0 %**	**2.15 [1.26, 3.68]**
Total events: 129 (MCS), 94 (AC)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 7.53, df = 7 (P = 0.38); I^2 =7%					
Test for overall effect: Z = 2.80 (P = 0.0052)					

Analysis 1.3. Comparison 1 MCS vs anticholinergics (AC), Outcome 3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved).

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 1 MCS vs anticholinergics (AC)

Outcome: 3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved)

Study or subgroup	MCS n/N	AC n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Children					
Boner 1987	12/15	10/15		27.1 %	2.00 [0.38, 10.51]
Godfrey 1976	11/15	2/7		18.7 %	6.88 [0.93, 50.78]
Subtotal (95% CI)	**30**	**22**		**45.8 %**	**3.31 [0.92, 11.86]**
Total events: 23 (MCS), 12 (AC)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.87$, df = 1 (P = 0.35); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.84 (P = 0.066)					
2 Adults					
Boulet 1889	6/11	5/11		26.5 %	1.44 [0.27, 7.71]
Dorward 1982	6/7	4/7		11.1 %	4.50 [0.34, 60.15]
Tullett 1982	6/8	4/8		16.6 %	3.00 [0.36, 24.92]
Subtotal (95% CI)	**26**	**26**		**54.2 %**	**2.28 [0.70, 7.36]**
Total events: 18 (MCS), 13 (AC)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.62$, df = 2 (P = 0.73); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.38 (P = 0.17)					
Total (95% CI)	**56**	**48**		**100.0 %**	**2.70 [1.14, 6.41]**
Total events: 41 (MCS), 25 (AC)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.66$, df = 4 (P = 0.80); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.26 (P = 0.024)					

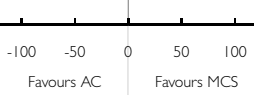
Analysis 1.4. Comparison 1 MCS vs anticholinergics (AC), Outcome 4 Mean degree of clinical protection: PFT comparison.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 1 MCS vs anticholinergics (AC)

Outcome: 4 Mean degree of clinical protection: PFT comparison

Study or subgroup	MCS N	Mean(SD)	AC N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Children							
Boner 1987	15	65.28 (21.56)	15	53.06 (28.95)		23.3 %	12.22 [-6.05, 30.49]
Godfrey 1976	15	60.05 (40.18)	7	29.96 (63.35)		3.0 %	30.09 [-21.06, 81.24]
Neijens 1981a	13	25.8 (14.78)	13	16.6 (14.78)		60.1 %	9.20 [-2.16, 20.56]
Subtotal (95% CI)	**43**		**35**			**86.3 %**	**10.73 [1.25, 20.21]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.65$, df = 2 (P = 0.72); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.22 (P = 0.027)							
2 Adults							
Boulet 1889	11	35.15 (55.36)	11	53.66 (44.29)		4.4 %	-18.51 [-60.41, 23.39]
Dorward 1982	7	77.27 (28.14)	7	42.75 (49.08)		4.4 %	34.52 [-7.39, 76.43]
Tullett 1982	8	71.19 (31.54)	8	45.67 (48.31)		4.9 %	25.52 [-14.46, 65.50]
Subtotal (95% CI)	**26**		**26**			**13.7 %**	**14.05 [-17.70, 45.79]**
Heterogeneity: $Tau^2 = 343.89$; $Chi^2 = 3.55$, df = 2 (P = 0.17); $I^2 = 44\%$							
Test for overall effect: Z = 0.87 (P = 0.39)							
Total (95% CI)	**69**		**61**			**100.0 %**	**11.21 [2.40, 20.02]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.27$, df = 5 (P = 0.51); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.49 (P = 0.013)							



Analysis 1.5. Comparison 1 MCS vs anticholinergics (AC), Outcome 5 ADRS.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 1 MCS vs anticholinergics (AC)

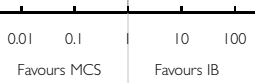
Outcome: 5 ADRS

Study or subgroup	MCS n/N	IB n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 General side effects				
Boner 1987	0/15	0/15		0.0 [0.0, 0.0]
Bundgaard 1980	0/18	0/18		0.0 [0.0, 0.0]
Thompson 1978	0/13	0/13		0.0 [0.0, 0.0]
Tullett 1982	0/8	0/8		0.0 [0.0, 0.0]
Total (95% CI)	**54**	**54**		**0.0 [0.0, 0.0]**

Total events: 0 (MCS), 0 (IB)

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

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



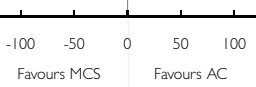
Analysis 1.6. Comparison 1 MCS vs anticholinergics (AC), Outcome 6 High vs low quality.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 1 MCS vs anticholinergics (AC)

Outcome: 6 High vs low quality

Study or subgroup	MSC N	Mean(SD)	AC N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Low quality (Jadad 1-2)							
Dorward 1982	7	8.86 (11.88)	7	23.57 (19.79)		3.9 %	-14.71 [-31.81, 2.39]
Godfrey 1976	15	19.33 (18.28)	7	24.57 (22.14)		3.2 %	-5.24 [-24.07, 13.59]
Spada 1985	100	4.44 (16.2)	100	9.88 (17.31)		52.4 %	-5.44 [-10.09, -0.79]
Tullett 1982	8	11.17 (11.48)	8	22.44 (25.07)		3.1 %	-11.27 [-30.38, 7.84]
Subtotal (95% CI)	**130**		**122**			**62.6 %**	**-6.29 [-10.54, -2.04]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.33$, df = 3 (P = 0.72); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.90 (P = 0.0037)							
2 High quality (Jadad 3-5)							
Boner 1987	15	15.5 (11.67)	15	21.73 (17.71)		9.8 %	-6.23 [-16.96, 4.50]
Neijens 1981a	13	6.7 (7.57)	13	12.5 (16.95)		11.1 %	-5.80 [-15.89, 4.29]
Thompson 1978	13	14.58 (21.08)	13	26.39 (19.66)		4.6 %	-11.81 [-27.48, 3.86]
Vazquez 1984	12	4.2 (6.8)	12	12.1 (15.9)		11.8 %	-7.90 [-17.68, 1.88]
Subtotal (95% CI)	**53**		**53**			**37.4 %**	**-7.32 [-12.82, -1.82]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.46$, df = 3 (P = 0.93); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.61 (P = 0.0091)							
Total (95% CI)	**183**		**175**			**100.0 %**	**-6.68 [-10.04, -3.31]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.87$, df = 7 (P = 0.97); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.89 (P = 0.00010)							



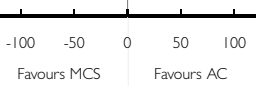
Analysis 1.7. Comparison 1 MCS vs anticholinergics (AC), Outcome 7 Effect by severity.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 1 MCS vs anticholinergics (AC)

Outcome: 7 Effect by severity

Study or subgroup	MCS N	MCS Mean(SD)	AC N	AC Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mild EIB (< 30% maximum fall on placebo)							
Neijens 1981a	13	6.7 (7.57)	13	12.5 (16.95)		11.1 %	-5.80 [-15.89, 4.29]
Spada 1985	100	4.44 (16.2)	100	9.88 (17.31)		52.4 %	-5.44 [-10.09, -0.79]
Vazquez 1984	12	4.2 (6.8)	12	12.1 (15.9)		11.8 %	-7.90 [-17.68, 1.88]
Subtotal (95% CI)	**125**		**125**			**75.4 %**	**-5.88 [-9.75, -2.00]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.20$, df = 2 (P = 0.91); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.97 (P = 0.0029)							
2 Severe EIB (=>30% maximum fall on placebo)							
Boner 1987	15	15.5 (11.67)	15	21.73 (17.71)		9.8 %	-6.23 [-16.96, 4.50]
Dorward 1982	7	8.86 (11.88)	7	23.57 (19.79)		3.9 %	-14.71 [-31.81, 2.39]
Godfrey 1976	15	19.33 (18.28)	7	24.57 (22.14)		3.2 %	-5.24 [-24.07, 13.59]
Thompson 1978	13	14.58 (21.08)	13	26.39 (19.66)		4.6 %	-11.81 [-27.48, 3.86]
Tullett 1982	8	11.17 (11.48)	8	22.44 (25.07)		3.1 %	-11.27 [-30.38, 7.84]
Subtotal (95% CI)	**58**		**50**			**24.6 %**	**-9.12 [-15.90, -2.33]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.01$, df = 4 (P = 0.91); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.63 (P = 0.0084)							
Total (95% CI)	**183**		**175**			**100.0 %**	**-6.68 [-10.04, -3.31]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.87$, df = 7 (P = 0.97); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.89 (P = 0.00010)							



Analysis 1.8. Comparison 1 MCS vs anticholinergics (AC), Outcome 8 Effect by steroid use.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 1 MCS vs anticholinergics (AC)

Outcome: 8 Effect by steroid use

Study or subgroup	MCS N	Mean(SD)	AC N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 No recent steroid use							
Boner 1987	15	15.5 (11.67)	15	21.73 (17.71)		30.2 %	-6.23 [-16.96, 4.50]
Dorward 1982	7	8.86 (11.88)	7	23.57 (19.79)		11.9 %	-14.71 [-31.81, 2.39]
Neijens 1981a	13	6.7 (7.57)	13	12.5 (16.95)		34.2 %	-5.80 [-15.89, 4.29]
Thompson 1978	13	14.58 (21.08)	13	26.39 (19.66)		14.2 %	-11.81 [-27.48, 3.86]
Tullett 1982	8	11.17 (11.48)	8	22.44 (25.07)		9.5 %	-11.27 [-30.38, 7.84]
Subtotal (95% CI)	**56**		**56**			**100.0 %**	**-8.36 [-14.26, -2.46]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.20$, df = 4 (P = 0.88); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.78 (P = 0.0055)							
2 Some on ICS (no studies)							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**56**		**56**			**100.0 %**	**-8.36 [-14.26, -2.46]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.20$, df = 4 (P = 0.88); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.78 (P = 0.0055)							

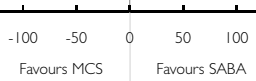
Analysis 2.1. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 1 Maximum percent decrease in PFT.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 1 Maximum percent decrease in PFT

Study or subgroup	MCS N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Children							
Debelic 1988	14	27.26 (20.34)	14	13.53 (28.08)		1.6 %	13.73 [-4.43, 31.89]
Godfrey 1976	15	19.33 (18.28)	15	3.73 (4.99)		5.4 %	15.60 [6.01, 25.19]
Neijens 1981a	13	6.7 (7.57)	13	1.5 (18.75)		4.2 %	5.20 [-5.79, 16.19]
Obata 1993	14	18.95 (13.74)	14	8.84 (16.38)		4.1 %	10.11 [-1.09, 21.31]
Pichaipat 1995	11	12.93 (3.59)	11	7.24 (5.4)		20.8 %	5.69 [1.86, 9.52]
Vazquez 1984	12	4.2 (6.8)	13	2.4 (7.2)		13.2 %	1.80 [-3.69, 7.29]
Zanconato 1990	12	12.6 (8.9)	12	2.5 (5.3)		12.0 %	10.10 [4.24, 15.96]
Subtotal (95% CI)	**91**		**92**			**61.4 %**	**7.30 [3.88, 10.73]**
Heterogeneity: Tau² = 6.48; Chi² = 8.93, df = 6 (P = 0.18); I² =33%							
Test for overall effect: Z = 4.18 (P = 0.000029)							
2 Adults							
Clarke 1990	20	13.41 (15.64)	20	2.62 (17.32)		4.8 %	10.79 [0.56, 21.02]
Gehrke 1986	8	22.3 (17.4)	8	6.9 (10.6)		2.7 %	15.40 [1.28, 29.52]
Rohr 1987	40	14 (15.49)	40	6 (17.32)		8.8 %	8.00 [0.80, 15.20]
Spada 1985	100	4.44 (17.55)	100	1 (9.3)		20.4 %	3.44 [-0.45, 7.33]
Woolley 1990	12	24.38 (24.25)	12	15.5 (17.32)		1.9 %	8.88 [-7.98, 25.74]
Subtotal (95% CI)	**180**		**180**			**38.6 %**	**6.39 [2.67, 10.12]**
Heterogeneity: Tau² = 2.71; Chi² = 4.59, df = 4 (P = 0.33); I² =13%							
Test for overall effect: Z = 3.36 (P = 0.00077)							
Total (95% CI)	**271**		**272**			**100.0 %**	**6.84 [4.47, 9.22]**
Heterogeneity: Tau² = 3.26; Chi² = 13.75, df = 11 (P = 0.25); I² =20%							
Test for overall effect: Z = 5.64 (P < 0.00001)							



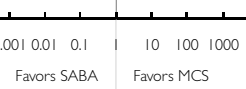
Analysis 2.2. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved).

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved)

Study or subgroup	MCS n/N	SABA n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 Children				
Debelic 1988	4/14	8/14		0.30 [0.06, 1.44]
Godfrey 1976	7/15	14/15		0.06 [0.01, 0.60]
Obata 1993	6/14	10/14		0.30 [0.06, 1.44]
Pichaipat 1995	8/11	11/11		0.11 [0.00, 2.33]
Svenonius 1988	3/7	7/7		0.05 [0.00, 1.25]
Vazquez 1984	12/12	13/13		0.0 [0.0, 0.0]
Subtotal (95% CI)	**73**	**74**		**0.18 [0.07, 0.46]**
Total events: 40 (MCS), 63 (SABA)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.38, df = 4 (P = 0.67); I^2 =0.0%				
Test for overall effect: Z = 3.64 (P = 0.00027)				
2 Adults				
Rohr 1987	26/40	36/40		0.21 [0.06, 0.70]
Spada 1985	81/100	89/100		0.53 [0.24, 1.17]
Woolley 1990	2/12	4/12		0.40 [0.06, 2.77]
Subtotal (95% CI)	**152**	**152**		**0.40 [0.21, 0.75]**
Total events: 109 (MCS), 129 (SABA)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.59, df = 2 (P = 0.45); I^2 =0.0%				
Test for overall effect: Z = 2.86 (P = 0.0043)				
Total (95% CI)	**225**	**226**		**0.31 [0.18, 0.52]**
Total events: 149 (MCS), 192 (SABA)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 5.82, df = 7 (P = 0.56); I^2 =0.0%				
Test for overall effect: Z = 4.42 (P < 0.00001)				



Analysis 2.3. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved).

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved)

Study or subgroup	MCS n/N	SABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Children					
Debelic 1988	8/14	9/14		23.4 %	0.74 [0.16, 3.39]
Godfrey 1976	11/15	15/15		6.0 %	0.08 [0.00, 1.69]
Obata 1993	6/14	11/14		19.7 %	0.20 [0.04, 1.07]
Pichaipat 1995	7/11	9/11		14.1 %	0.39 [0.05, 2.77]
Subtotal (95% CI)	**54**	**54**		**63.2 %**	**0.35 [0.14, 0.88]**
Total events: 32 (MCS), 44 (SABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.25$, df = 3 (P = 0.52); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.23 (P = 0.026)					
2 Adults					
Boulet 1889	6/11	8/11		17.1 %	0.45 [0.08, 2.67]
Woolley 1990	4/12	7/12		19.7 %	0.36 [0.07, 1.88]
Subtotal (95% CI)	**23**	**23**		**36.8 %**	**0.40 [0.12, 1.34]**
Total events: 10 (MCS), 15 (SABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.85); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.49 (P = 0.14)					
Total (95% CI)	**77**	**77**		**100.0 %**	**0.37 [0.18, 0.77]**
Total events: 42 (MCS), 59 (SABA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.31$, df = 5 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.67 (P = 0.0075)					

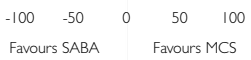
Analysis 2.4. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 4 Mean degree of protection: PFT comparison.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 4 Mean degree of protection: PFT comparison

Study or subgroup	MCS N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Children							
Debelic 1988	14	33.2 (54.54)	14	75.65 (66.83)		4.8 %	-42.45 [-87.64, 2.74]
Godfrey 1976	15	60.05 (40.18)	15	92.37 (10.31)		14.6 %	-32.32 [-53.31, -11.33]
Neijens 1981a	13	25.8 (14.78)	13	32.5 (5.4)		27.3 %	-6.70 [-15.25, 1.85]
Obata 1993	14	54.71 (19.72)	14	81.09 (27.74)		17.3 %	-26.38 [-44.21, -8.55]
Pichaipat 1995	11	51.54 (18.96)	11	74.56 (19.23)		19.1 %	-23.02 [-38.98, -7.06]
Subtotal (95% CI)	**67**		**67**			**83.2 %**	**-21.55 [-34.15, -8.96]**
Heterogeneity: Tau^2 = 112.91; Chi^2 = 10.18, df = 4 (P = 0.04); I^2 =61%							
Test for overall effect: Z = 3.35 (P = 0.00080)							
2 Adults							
Boulet 1889	11	35.15 (55.36)	11	71.54 (28.96)		6.7 %	-36.39 [-73.31, 0.53]
Woolley 1990	12	27.76 (38.23)	12	54.07 (32.33)		10.0 %	-26.31 [-54.64, 2.02]
Subtotal (95% CI)	**23**		**23**			**16.8 %**	**-30.05 [-52.52, -7.57]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.18, df = 1 (P = 0.67); I^2 =0.0%							
Test for overall effect: Z = 2.62 (P = 0.0088)							
Total (95% CI)	**90**		**90**			**100.0 %**	**-22.67 [-33.42, -11.92]**
Heterogeneity: Tau^2 = 90.89; Chi^2 = 11.89, df = 6 (P = 0.06); I^2 =50%							
Test for overall effect: Z = 4.13 (P = 0.000036)							



Analysis 2.5. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 5 ADRS.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 5 ADRS

Study or subgroup	MCS n/N	SABA n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 General side effects				
Boner 1987	0/1	0/1		0.0 [0.0, 0.0]
Bundgaard 1980	0/18	10/18		0.02 [0.00, 0.42]
Bundgaard 1983p	0/17	0/17		0.0 [0.0, 0.0]
Clarke 1990	0/20	0/20		0.0 [0.0, 0.0]
Debelic 1988	0/14	0/14		0.0 [0.0, 0.0]
Gehrke 1986	1/8	7/8		0.02 [0.00, 0.40]
Obata 1993	0/14	0/14		0.0 [0.0, 0.0]
Rohr 1987	0/40	0/40		0.0 [0.0, 0.0]
Tullett 1982	0/8	0/8		0.0 [0.0, 0.0]
Woolley 1990	3/12	0/12		9.21 [0.42, 200.59]
Total (95% CI)	**152**	**152**		**0.16 [0.00, 8.24]**

Total events: 4 (MCS), 17 (SABA)

Heterogeneity: $Tau^2 = 9.92$; $Chi^2 = 10.48$, df = 2 (P = 0.01); $I^2 = 81\%$

Test for overall effect: Z = 0.92 (P = 0.36)

Analysis 2.6. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 6 High vs low quality.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 6 High vs low quality

Study or subgroup	MCS N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Low quality (Jadad 1-2)							
Godfrey 1976	15	19.33 (18.28)	15	3.73 (4.99)		5.6 %	15.60 [6.01, 25.19]
Pichaipat 1995	11	12.93 (3.59)	11	7.24 (5.4)		19.6 %	5.69 [1.86, 9.52]
Rohr 1987	40	15.64 (15.49)	40	6 (17.32)		8.9 %	9.64 [2.44, 16.84]
Spada 1985	100	4.44 (16.2)	100	1 (9.3)		20.5 %	3.44 [-0.22, 7.10]
Zanconato 1990	12	12.6 (8.9)	12	2.5 (5.3)		12.0 %	10.10 [4.24, 15.96]
Subtotal (95% CI)	**178**		**178**			**66.6 %**	**7.51 [3.97, 11.04]**
Heterogeneity: Tau² = 8.07; Chi² = 8.49, df = 4 (P = 0.08); I² =53%							
Test for overall effect: Z = 4.16 (P = 0.000032)							
2 High quality (Jadad 3-5)							
Clarke 1990	20	13.41 (15.64)	20	2.62 (17.32)		5.0 %	10.79 [0.56, 21.02]
Debelic 1988	14	27.26 (20.34)	14	13.53 (28.08)		1.7 %	13.73 [-4.43, 31.89]
Gehrke 1986	8	22.3 (17.4)	8	6.9 (10.6)		2.8 %	15.40 [1.28, 29.52]
Neijens 1981a	13	6.7 (7.57)	13	1.5 (18.75)		4.4 %	5.20 [-5.79, 16.19]
Obata 1993	14	18.95 (13.74)	14	8.84 (16.38)		4.3 %	10.11 [-1.09, 21.31]
Vazquez 1984	12	4.2 (6.8)	13	2.4 (7.2)		13.1 %	1.80 [-3.69, 7.29]
Woolley 1990	12	24.38 (24.25)	12	15.5 (17.32)		2.0 %	8.88 [-7.98, 25.74]
Subtotal (95% CI)	**93**		**94**			**33.4 %**	**6.32 [2.47, 10.18]**
Heterogeneity: Tau² = 0.67; Chi² = 6.13, df = 6 (P = 0.41); I² =2%							
Test for overall effect: Z = 3.21 (P = 0.0013)							
Total (95% CI)	**271**		**272**			**100.0 %**	**7.06 [4.60, 9.52]**
Heterogeneity: Tau² = 4.19; Chi² = 14.63, df = 11 (P = 0.20); I² =25%							
Test for overall effect: Z = 5.62 (P < 0.00001)							

Analysis 2.7. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 7 Effect by severity.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 7 Effect by severity

Study or subgroup	MCS N	MCS Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mild EIB (< 30% maximum fall on placebo)							
Neijens 1981a	13	6.7 (7.57)	13	1.5 (18.75)		4.3 %	5.20 [-5.79, 16.19]
Pichaipat 1995	11	12.93 (3.59)	11	7.24 (5.4)		20.2 %	5.69 [1.86, 9.52]
Spada 1985	100	4.44 (16.2)	100	1 (9.3)		21.1 %	3.44 [-0.22, 7.10]
Vazquez 1984	12	4.2 (6.8)	13	2.4 (7.2)		13.1 %	1.80 [-3.69, 7.29]
Subtotal (95% CI)	**136**		**137**			**58.7 %**	**4.06 [1.73, 6.39]**
Heterogeneity: Tau² = 0.0; Chi² = 1.50, df = 3 (P = 0.68); I² =0.0%							
Test for overall effect: Z = 3.41 (P = 0.00065)							
2 Severe EIB (=>30% maximum fall on placebo)							
Clarke 1990	20	13.41 (15.64)	20	2.38 (17.32)		4.9 %	11.03 [0.80, 21.26]
Debelic 1988	14	27.26 (20.34)	14	13.53 (28.08)		1.7 %	13.73 [-4.43, 31.89]
Gehrke 1986	8	22.3 (17.4)	8	6.9 (10.6)		2.7 %	15.40 [1.28, 29.52]
Godfrey 1976	15	19.33 (18.28)	15	3.73 (4.99)		5.4 %	15.60 [6.01, 25.19]
Obata 1993	14	18.95 (13.74)	14	8.84 (16.38)		4.1 %	10.11 [-1.09, 21.31]
Rohr 1987	40	14 (15.64)	40	6 (17.32)		8.7 %	8.00 [0.77, 15.23]
Woolley 1990	12	24.38 (24.25)	12	15.5 (17.32)		1.9 %	8.88 [-7.98, 25.74]
Zanconato 1990	12	12.6 (8.9)	12	2.5 (5.3)		11.9 %	10.10 [4.24, 15.96]
Subtotal (95% CI)	**135**		**135**			**41.3 %**	**10.80 [7.44, 14.17]**
Heterogeneity: Tau² = 0.0; Chi² = 2.17, df = 7 (P = 0.95); I² =0.0%							
Test for overall effect: Z = 6.29 (P < 0.00001)							
Total (95% CI)	**271**		**272**			**100.0 %**	**6.85 [4.45, 9.24]**
Heterogeneity: Tau² = 3.58; Chi² = 14.09, df = 11 (P = 0.23); I² =22%							
Test for overall effect: Z = 5.60 (P < 0.00001)							

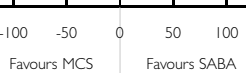
Analysis 2.8. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 8 By delivery method.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 8 By delivery method

Study or subgroup	MCS N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 MDI							
Debelic 1988	14	27.26 (20.34)	14	13.53 (28.08)		3.0 %	13.73 [-4.43, 31.89]
Woolley 1990	12	24.38 (24.25)	12	15.5 (17.32)		3.4 %	8.88 [-7.98, 25.74]
Subtotal (95% CI)	**26**		**26**			**6.5 %**	**11.12 [-1.23, 23.48]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.76 (P = 0.078)							
2 Spinhaler (Top/Bottom Index)							
Bundgaard 1983a	15	28 (15.49)	15	7 (4.15)		9.0 %	21.00 [12.88, 29.12]
Bundgaard 1983p	17	20 (12.36)	17	7 (4.12)		11.3 %	13.00 [6.81, 19.19]
Bundgaard 1986pdr	16	25 (11.43)	16	9 (2.86)		11.9 %	16.00 [10.23, 21.77]
Subtotal (95% CI)	**48**		**48**			**32.3 %**	**16.05 [11.95, 20.15]**
Heterogeneity: $Tau^2 = 2.04$; $Chi^2 = 2.36$, df = 2 (P = 0.31); $I^2 = 15\%$							
Test for overall effect: Z = 7.67 (P < 0.00001)							
3 Nebulisation							
Obata 1993	14	18.95 (13.74)	14	8.84 (16.38)		6.2 %	10.11 [-1.09, 21.31]
Vazquez 1984	12	4.2 (6.8)	13	2.4 (7.2)		12.3 %	1.80 [-3.69, 7.29]
Subtotal (95% CI)	**26**		**27**			**18.5 %**	**4.46 [-3.14, 12.06]**
Heterogeneity: $Tau^2 = 14.28$; $Chi^2 = 1.71$, df = 1 (P = 0.19); $I^2 = 41\%$							
Test for overall effect: Z = 1.15 (P = 0.25)							
4 Two or more methods							
Clarke 1990	20	13.41 (15.64)	20	2.38 (17.32)		7.0 %	11.03 [0.80, 21.26]
Godfrey 1976	15	19.33 (18.28)	15	3.73 (4.99)		7.5 %	15.60 [6.01, 25.19]
Neijens 1981a	13	6.7 (7.57)	13	1.5 (18.75)		6.4 %	5.20 [-5.79, 16.19]
Rohr 1987	40	14 (15.64)	40	6 (17.32)		10.0 %	8.00 [0.77, 15.23]
Zanconato 1990	12	12.6 (8.9)	12	2.5 (5.3)		11.8 %	10.10 [4.24, 15.96]
Subtotal (95% CI)	**100**		**100**			**42.7 %**	**9.94 [6.34, 13.55]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.38$, df = 4 (P = 0.67); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.41 (P < 0.00001)							
Total (95% CI)	**200**		**201**			**100.0 %**	**11.12 [7.65, 14.59]**
Heterogeneity: $Tau^2 = 17.69$; $Chi^2 = 22.76$, df = 11 (P = 0.02); $I^2 = 52\%$							
Test for overall effect: Z = 6.27 (P < 0.00001)							



Analysis 2.9. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 9 By Drug: MSC vs SABA.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 9 By Drug: MSC vs SABA

Study or subgroup	MSC N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Fenoterol							
Clarke 1990	20	13.41 (15.64)	20	2.38 (17.32)		5.2 %	11.03 [0.80, 21.26]
Gehrke 1986	8	22.3 (17.4)	8	6.9 (10.6)		3.5 %	15.40 [1.28, 29.52]
Neijens 1981a	13	6.7 (7.57)	13	1.5 (18.75)		4.8 %	5.20 [-5.79, 16.19]
Subtotal (95% CI)	**41**		**41**			**13.5 %**	**9.88 [3.26, 16.49]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.33$, df = 2 (P = 0.51); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.93 (P = 0.0034)							
2 Salbutamol							
Godfrey 1976	15	19.33 (18.28)	15	3.73 (4.99)		5.5 %	15.60 [6.01, 25.19]
Rohr 1987	40	14 (15.64)	40	6 (17.32)		7.0 %	8.00 [0.77, 15.23]
Vazquez 1984	12	4.2 (6.8)	13	2.4 (7.2)		8.2 %	1.80 [-3.69, 7.29]
Zanconato 1990	12	12.6 (8.9)	12	2.5 (5.3)		7.9 %	10.10 [4.24, 15.96]
Subtotal (95% CI)	**79**		**80**			**28.7 %**	**8.15 [2.71, 13.59]**
Heterogeneity: $Tau^2 = 18.35$; $Chi^2 = 7.65$, df = 3 (P = 0.05); $I^2 = 61\%$							
Test for overall effect: Z = 2.94 (P = 0.0033)							
3 Terbutaline							
Pichaipat 1995	11	12.93 (3.59)	11	7.24 (5.4)		9.3 %	5.69 [1.86, 9.52]
Woolley 1990	12	24.38 (24.25)	12	15.5 (17.32)		2.7 %	8.88 [-7.98, 25.74]
Subtotal (95% CI)	**23**		**23**			**12.1 %**	**5.85 [2.11, 9.58]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.07 (P = 0.0022)							
4 Reproterol/procaterol							
Debelic 1988	14	27.26 (20.34)	14	13.53 (28.08)		2.4 %	13.73 [-4.43, 31.89]
Obata 1993	14	18.95 (13.74)	14	8.84 (16.38)		4.7 %	10.11 [-1.09, 21.31]
Subtotal (95% CI)	**28**		**28**			**7.1 %**	**11.11 [1.57, 20.64]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0.0\%$							

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Study or subgroup	MSC N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 2.28 (P = 0.022)							
5 Fenoterol (Top/Bottom Index)							
Bundgaard 1980	18	22.5 (10.61)	18	3.13 (2.65)		8.5 %	19.37 [14.32, 24.42]
Bundgaard 1983a	15	28 (15.49)	15	7 (4.15)		6.4 %	21.00 [12.88, 29.12]
Bundgaard 1983p	17	20 (12.36)	17	7 (4.12)		7.7 %	13.00 [6.81, 19.19]
Subtotal (95% CI)	**50**		**50**			**22.6 %**	**17.60 [12.95, 22.24]**
Heterogeneity: Tau² = 6.58; Chi² = 3.26, df = 2 (P = 0.20); I² =39%							
Test for overall effect: Z = 7.43 (P < 0.00001)							
6 Salbutamol (Top/Bottom Index)							
Bundgaard 1986neb	16	14 (8.33)	16	9 (8.33)		8.0 %	5.00 [-0.77, 10.77]
Bundgaard 1986pdr	16	25 (11.43)	16	9 (2.86)		8.0 %	16.00 [10.23, 21.77]
Subtotal (95% CI)	**32**		**32**			**16.0 %**	**10.50 [-0.28, 21.28]**
Heterogeneity: Tau² = 51.82; Chi² = 6.97, df = 1 (P = 0.01); I² =86%							
Test for overall effect: Z = 1.91 (P = 0.056)							
Total (95% CI)	**253**		**254**			**100.0 %**	**11.00 [7.76, 14.23]**
Heterogeneity: Tau² = 25.37; Chi² = 44.63, df = 15 (P = 0.00009); I² =66%							
Test for overall effect: Z = 6.66 (P < 0.00001)							

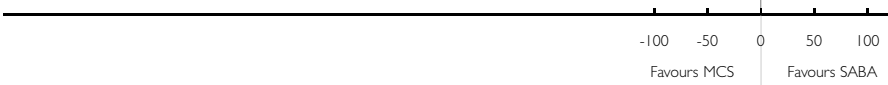
Analysis 2.10. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 10 By method used to calculate change.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 10 By method used to calculate change

Study or subgroup	MCS N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Percent Change Index							
Clarke 1990	20	13.41 (15.64)	20	2.62 (17.32)		8.4 %	10.79 [0.56, 21.02]
Debelic 1988	14	27.26 (20.34)	14	13.53 (28.08)		4.0 %	13.73 [-4.43, 31.89]
Gehrke 1986	8	22.3 (17.4)	8	6.9 (10.6)		5.7 %	15.40 [1.28, 29.52]
Godfrey 1976	15	19.33 (18.28)	15	3.73 (4.99)		9.0 %	15.60 [6.01, 25.19]
Neijens 1981a	13	6.7 (7.57)	13	1.5 (18.75)		7.8 %	5.20 [-5.79, 16.19]
Obata 1993	14	18.95 (13.74)	14	8.84 (16.38)		7.6 %	10.11 [-1.09, 21.31]
Pichaipat 1995	11	12.93 (3.59)	11	7.24 (5.4)		15.3 %	5.69 [1.86, 9.52]
Rohr 1987	40	15.64 (15.49)	40	6 (17.32)		11.4 %	9.64 [2.44, 16.84]
Vazquez 1984	12	4.2 (6.8)	13	2.4 (7.2)		13.4 %	1.80 [-3.69, 7.29]
Woolley 1990	12	24.38 (24.25)	12	15.5 (17.32)		4.4 %	8.88 [-7.98, 25.74]
Zanconato 1990	12	12.6 (8.9)	12	2.5 (5.3)		13.0 %	10.10 [4.24, 15.96]
Subtotal (95% CI)	**171**		**172**			**100.0 %**	**7.76 [5.23, 10.30]**
Heterogeneity: Tau^2 = 2.09; Chi^2 = 11.29, df = 10 (P = 0.34); I^2 =11%							
Test for overall effect: Z = 6.01 (P < 0.00001)							
2 Top-Bottom Index							
Bundgaard 1980	18	22.5 (10.61)	18	3.13 (2.65)		22.1 %	19.37 [14.32, 24.42]
Bundgaard 1983a	15	28 (15.49)	15	7 (4.15)		16.6 %	21.00 [12.88, 29.12]
Bundgaard 1983p	17	20 (12.36)	17	7 (4.12)		19.9 %	13.00 [6.81, 19.19]
Bundgaard 1986neb	16	14 (8.33)	16	9 (8.33)		20.7 %	5.00 [-0.77, 10.77]
Bundgaard 1986pdr	16	25 (11.43)	16	9 (2.86)		20.7 %	16.00 [10.23, 21.77]
Subtotal (95% CI)	**82**		**82**			**100.0 %**	**14.71 [9.14, 20.29]**
Heterogeneity: Tau^2 = 30.52; Chi^2 = 16.92, df = 4 (P = 0.002); I^2 =76%							
Test for overall effect: Z = 5.17 (P < 0.00001)							



Analysis 2.11. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 11 Effect by severity (TBI).

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 11 Effect by severity (TBI)

Study or subgroup	MCS N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
3 Top/Bottom index (Severe EIB)							
Bundgaard 1980	18	22.5 (10.61)	18	3.13 (2.65)		26.7 %	19.37 [14.32, 24.42]
Bundgaard 1983a	15	28 (15.49)	15	7 (4.15)		22.0 %	21.00 [12.88, 29.12]
Bundgaard 1986neb	16	14 (8.33)	16	9 (8.33)		25.6 %	5.00 [-0.77, 10.77]
Bundgaard 1986pdr	16	25 (11.43)	16	9 (2.86)		25.6 %	16.00 [10.23, 21.77]
Subtotal (95% CI)	**65**		**65**			**100.0 %**	**15.18 [8.07, 22.29]**

Heterogeneity: $Tau^2 = 42.60$; $Chi^2 = 16.62$, df = 3 (P = 0.00085); $I^2 = 82\%$

Test for overall effect: Z = 4.19 (P = 0.000028)

Analysis 2.12. Comparison 2 MCS vs short acting beta-agonist (SABA), Outcome 12 Effect by steroid use.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 2 MCS vs short acting beta-agonist (SABA)

Outcome: 12 Effect by steroid use

Study or subgroup	MCS N	MCS Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 No recent steroid use							
Debelic 1988	14	27.26 (20.34)	14	13.53 (28.08)		2.2 %	13.73 [-4.43, 31.89]
Neijens 1981a	13	6.7 (7.57)	13	1.5 (18.75)		5.9 %	5.20 [-5.79, 16.19]
Pichaipat 1995	11	12.93 (3.59)	11	7.24 (5.4)		48.9 %	5.69 [1.86, 9.52]
Rohr 1987	40	14 (15.49)	40	6 (17.32)		13.8 %	8.00 [0.80, 15.20]
Subtotal (95% CI)	**78**		**78**			**70.9 %**	**6.35 [3.16, 9.53]**
Heterogeneity: Tau² = 0.0; Chi² = 0.99, df = 3 (P = 0.80); I² =0.0%							
Test for overall effect: Z = 3.91 (P = 0.000093)							
2 Some on ICS							
Obata 1993	14	18.95 (13.74)	14	8.84 (16.38)		5.7 %	10.11 [-1.09, 21.31]
Woolley 1990	12	24.38 (24.25)	12	15.5 (17.32)		2.5 %	8.88 [-7.98, 25.74]
Zanconato 1990	12	12.6 (8.9)	12	2.5 (5.3)		20.9 %	10.10 [4.24, 15.96]
Subtotal (95% CI)	**38**		**38**			**29.1 %**	**10.00 [5.03, 14.96]**
Heterogeneity: Tau² = 0.0; Chi² = 0.02, df = 2 (P = 0.99); I² =0.0%							
Test for overall effect: Z = 3.95 (P = 0.000079)							
Total (95% CI)	**116**		**116**			**100.0 %**	**7.41 [4.73, 10.09]**
Heterogeneity: Tau² = 0.0; Chi² = 2.48, df = 6 (P = 0.87); I² =0.0%							
Test for overall effect: Z = 5.42 (P < 0.00001)							

Analysis 3.1. Comparison 3 SABA vs combination SABA + MCS, Outcome 1 Maximum percent decrease in PFT.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 3 SABA vs combination SABA + MCS

Outcome: 1 Maximum percent decrease in PFT

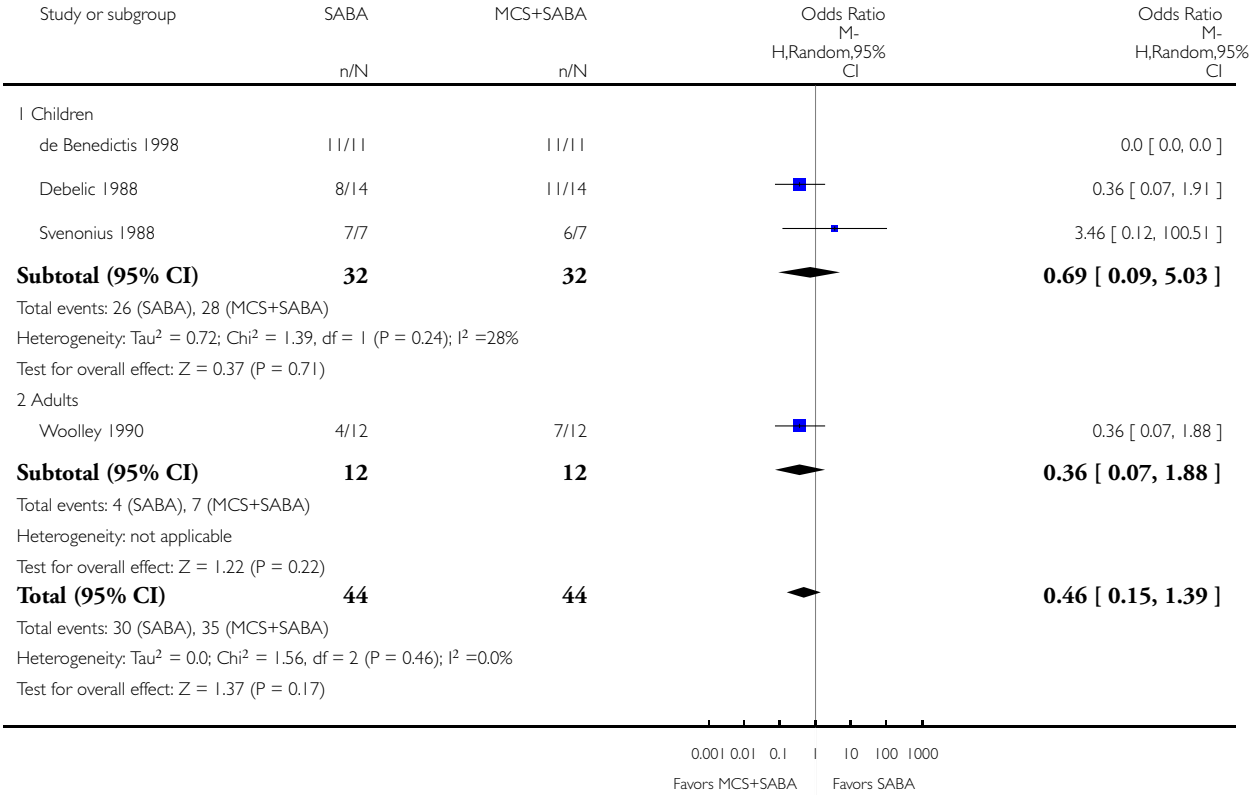
Study or subgroup	SABA N	Mean(SD)	MCS+B2 N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Children							
de Benedictis 1998	11	4.09 (4.48)	11	2.45 (2.81)		97.6 %	1.64 [-1.49, 4.77]
Debelic 1988	14	13.53 (28.08)	14	3.89 (25.45)		2.4 %	9.64 [-10.21, 29.49]
Subtotal (95% CI)	**25**		**25**			**100.0 %**	**1.83 [-1.25, 4.92]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.61$, df = 1 (P = 0.44); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.16 (P = 0.24)							
2 Adults							
Clarke 1990	20	2.62 (20.4)	20	3.33 (17.73)		41.2 %	-0.71 [-12.56, 11.14]
Gehrke 1986	8	20.2 (21.3)	8	16.4 (19.2)		14.6 %	3.80 [-16.07, 23.67]
Woolley 1990	12	15.5 (17.32)	12	13.13 (10.39)		44.2 %	2.37 [-9.06, 13.80]
Subtotal (95% CI)	**40**		**40**			**100.0 %**	**1.31 [-6.29, 8.91]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.21$, df = 2 (P = 0.90); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.34 (P = 0.74)							

Analysis 3.2. Comparison 3 SABA vs combination SABA + MCS, Outcome 2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved).

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 3 SABA vs combination SABA + MCS

Outcome: 2 Complete protection: post exercise fall PFT <15% (entered as proportion achieved)



Analysis 3.3. Comparison 3 SABA vs combination SABA + MCS, Outcome 3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved).

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 3 SABA vs combination SABA + MCS

Outcome: 3 Clinical Protection: 50% improvement over placebo (entered as proportion achieved)

Study or subgroup	SABA n/N	MCS+SABA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Children					
de Benedictis 1998	10/11	11/11		12.8 %	0.30 [0.01, 8.32]
Debelic 1988	9/14	12/14		40.8 %	0.30 [0.05, 1.91]
Subtotal (95% CI)	**25**	**25**		**53.6 %**	**0.30 [0.06, 1.52]**
Total events: 19 (SABA), 23 (MCS+SABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 1.46 (P = 0.15)					
2 Adults					
Woolley 1990	7/12	9/12		46.4 %	0.47 [0.08, 2.66]
Subtotal (95% CI)	**12**	**12**		**46.4 %**	**0.47 [0.08, 2.66]**
Total events: 7 (SABA), 9 (MCS+SABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					
Total (95% CI)	**37**	**37**		**100.0 %**	**0.37 [0.11, 1.21]**
Total events: 26 (SABA), 32 (MCS+SABA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.13, df = 2 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 1.65 (P = 0.099)					

Analysis 3.4. Comparison 3 SABA vs combination SABA + MCS, Outcome 4 Mean degree of protection: PFT comparison.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 3 SABA vs combination SABA + MCS

Outcome: 4 Mean degree of protection: PFT comparison

Study or subgroup	SABA N	Mean(SD)	MCS+SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Children						
de Benedictis 1998	11	79 (25.45)	11	88.18 (15.78)		-9.18 [-26.88, 8.52]
Debelic 1988	14	75.65 (66.83)	15	94.97 (74.15)		-19.32 [-70.64, 32.00]
Subtotal (95% CI)	**25**		**26**			**-10.26 [-26.99, 6.47]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.71); $I^2 = 0.0\%$						
Test for overall effect: Z = 1.20 (P = 0.23)						
2 Adults						
Woolley 1990	12	54.07 (0)	12	61.1 (0)		0.0 [0.0, 0.0]
Subtotal (95% CI)	**12**		**12**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Total (95% CI)	**37**		**38**			**-10.26 [-26.99, 6.47]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.71); $I^2 = 0.0\%$						
Test for overall effect: Z = 1.20 (P = 0.23)						

Analysis 3.5. Comparison 3 SABA vs combination SABA + MCS, Outcome 5 ADRS.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 3 SABA vs combination SABA + MCS

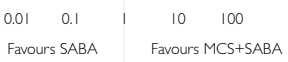
Outcome: 5 ADRS

Study or subgroup	SABA n/N	MCS+SABA n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 General side effects				
Bundgaard 1983p	0/17	0/17		0.0 [0.0, 0.0]
Clarke 1990	0/20	0/20		0.0 [0.0, 0.0]
de Benedictis 1998	0/11	0/11		0.0 [0.0, 0.0]
Debelic 1988	0/14	0/14		0.0 [0.0, 0.0]
Gehrke 1986	4/8	4/8		1.00 [0.14, 7.10]
Woolley 1990	0/12	0/12		0.0 [0.0, 0.0]
Total (95% CI)	**82**	**82**		**1.00 [0.14, 7.10]**

Total events: 4 (SABA), 4 (MCS+SABA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.0 (P = 1.0)



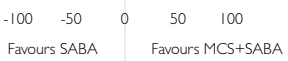
Analysis 3.6. Comparison 3 SABA vs combination SABA + MCS, Outcome 6 Effect by severity.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 3 SABA vs combination SABA + MCS

Outcome: 6 Effect by severity

Study or subgroup	SABA N	Mean(SD)	MSC+SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mild EIB (< 30% maximum fall on placebo)							
Clarke 1990	20	2.62 (20.4)	20	3.33 (17.73)		5.8 %	-0.71 [-12.56, 11.14]
de Benedictis 1998	11	4.09 (4.48)	11	2.45 (2.81)		83.8 %	1.64 [-1.49, 4.77]
Subtotal (95% CI)	**31**		**31**			**89.6 %**	**1.49 [-1.53, 4.51]**
Heterogeneity: Tau² = 0.0; Chi² = 0.14, df = 1 (P = 0.71); I² =0.0%							
Test for overall effect: Z = 0.96 (P = 0.33)							
2 Severe EIB (=>30% maximum fall on placebo)							
Debelic 1988	14	13.53 (28.08)	14	3.89 (25.45)		2.1 %	9.64 [-10.21, 29.49]
Gehrke 1986	8	20.2 (21.3)	8	16.4 (19.2)		2.1 %	3.80 [-16.07, 23.67]
Woolley 1990	12	15.5 (17.32)	12	13.13 (10.39)		6.3 %	2.37 [-9.06, 13.80]
Subtotal (95% CI)	**34**		**34**			**10.4 %**	**4.10 [-4.76, 12.97]**
Heterogeneity: Tau² = 0.0; Chi² = 0.39, df = 2 (P = 0.82); I² =0.0%							
Test for overall effect: Z = 0.91 (P = 0.36)							
Total (95% CI)	**65**		**65**			**100.0 %**	**1.76 [-1.10, 4.62]**
Heterogeneity: Tau² = 0.0; Chi² = 0.83, df = 4 (P = 0.93); I² =0.0%							
Test for overall effect: Z = 1.21 (P = 0.23)							



Analysis 3.7. Comparison 3 SABA vs combination SABA + MCS, Outcome 7 By method used to calculate change.

Review: Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction

Comparison: 3 SABA vs combination SABA + MCS

Outcome: 7 By method used to calculate change

Study or subgroup	SABA N	Mean(SD)	MCS+SABA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Percent Change Index							
Clarke 1990	20	2.62 (20.4)	20	3.33 (17.73)		1.1 %	-0.71 [-12.56, 11.14]
de Benedictis 1998	11	4.09 (4.48)	11	2.45 (2.81)		15.4 %	1.64 [-1.49, 4.77]
Debelic 1988	14	13.53 (28.08)	14	3.89 (25.45)		0.4 %	9.64 [-10.21, 29.49]
Gehrke 1986	8	20.2 (21.3)	8	16.4 (19.2)		0.4 %	3.80 [-16.07, 23.67]
Woolley 1990	12	15.5 (17.32)	12	13.13 (10.39)		1.2 %	2.37 [-9.06, 13.80]
Subtotal (95% CI)	**65**		**65**			**18.4 %**	**1.76 [-1.10, 4.62]**
Heterogeneity: Tau² = 0.0; Chi² = 0.83, df = 4 (P = 0.93); I² =0.0%							
Test for overall effect: Z = 1.21 (P = 0.23)							
2 Top/Bottom index							
Bundgaard 1983a	15	7 (4.15)	15	8 (4.15)		17.1 %	-1.00 [-3.97, 1.97]
Bundgaard 1983p	17	7 (4.12)	17	6 (4.12)		19.6 %	1.00 [-1.77, 3.77]
Bundgaard 1986neb	16	9 (8.33)	16	8 (5)		6.6 %	1.00 [-3.76, 5.76]
Bundgaard 1986pdr	16	9 (2.86)	16	9 (2.86)		38.3 %	0.0 [-1.98, 1.98]
Subtotal (95% CI)	**64**		**64**			**81.6 %**	**0.11 [-1.25, 1.47]**
Heterogeneity: Tau² = 0.0; Chi² = 1.08, df = 3 (P = 0.78); I² =0.0%							
Test for overall effect: Z = 0.16 (P = 0.87)							
Total (95% CI)	**129**		**129**			**100.0 %**	**0.42 [-0.81, 1.64]**
Heterogeneity: Tau² = 0.0; Chi² = 2.95, df = 8 (P = 0.94); I² =0.0%							
Test for overall effect: Z = 0.66 (P = 0.51)							

WHAT'S NEW

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

Date	Event	Description
27 April 2009	Amended	Technical issue identified; resolved by programmer

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 4, 2003

Date	Event	Description
8 August 2008	New search has been performed	Literature search re-run; no new studies identified.
7 August 2008	Amended	Converted to new review format.
29 May 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

C Spooner: initiated and conducted review; RS: co-reviewer, protocol development, study selection, quality scoring, editing; BHR: Assigned ARG Editor, co-reviewer, reviewed protocol, editing.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Division of Emergency Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada.
- Department of Family Medicine, Universiy of Alberta, Canada.

External sources

- Canadian Association of Emergency Medicine Research Consortium, Canada.
- Canadian Institute of Health Research (CIHR), Canada.
- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [*therapeutic use]; Asthma, Exercise-Induced [*prevention & control]; Bronchoconstriction [*drug effects]; Cholinergic Antagonists [*therapeutic use]; Mast Cells [*drug effects; physiology]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans