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Exercise-Induced Bronchoconstriction and Asthma

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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We thank Jennifer Seida for her work in developing the protocol, Mohammad Karkhaneh and Kate O'Gorman for assistance with data extraction and preparation of the appendices, Ken Bond for copyediting, and Simon Bow and Annabritt Chisholm for their assistance with literature retrieval.

Structured Abstract

Objectives: The objectives are: (1) to assess diagnostic test characteristics of six alternative index tests compared with the selected reference standard–a standardized exercise challenge test (ECT) in patients with suspected exercise-induced bronchoconstriction or asthma (EIB/EIA); (2) to determine the efficacy of a single prophylactic dose of four pharmacologic and one nonpharmacologic interventions versus placebo to attenuate EIB/EIA in patients with diagnosed EIB/EIA; and (3) to determine if regular daily treatment with short-acting or long-acting beta-agonists (SABA or LABA) causes patients with EIA to develop tachyphylaxis when additional prophylactic doses are used pre-exercise.

Data Sources: A systematic and comprehensive literature search was conducted in 14 electronic databases (Diagnosis) and the Cochrane Airways Register (Therapy).

Review Methods: Study selection, quality assessment, and data extraction were conducted independently by two reviewers. The primary outcome was the maximum percent fall in the post-exercise forced expiratory volume in 1 second (percent fall FEV_1). The diagnostic threshold for a positive ECT was a percent fall FEV_1 of 10 percent or more. Sensitivity (SN) and specificity (SP) were calculated. For therapy, mean differences (MD) in the percent fall FEV_1 and 95 percent confidence intervals (CI) (random effects model) were calculated. A positive MD indicates the intervention works better than the control.

Results: For the diagnostic reviews, 5,318 citations yielded 28 relevant studies; for the therapy reviews, 1,634 citations yielded 109 relevant RCTs

Diagnostic test results versus ECT: self-reported history (2 studies) SN=36–89 percent, SP=85–86 percent; methacholine challenge (16 studies) SN=0–100 percent, SP=0–100 percent; sport specific challenges (5 studies) SN=0–100 percent, SP=0–100 percent; eucapnic voluntary hyperpnea (7 studies) SN=25–90 percent, SP=0–71 percent; free running asthma screening test (3 studies) SN=60–67 percent, SP=47–67 percent; mannitol (3 studies) SN=58–96 percent, SP=65-78 percent. All SN and SP calculations indicated substantial heterogeneity that could not be explained by sensitivity or subgroup analyses.

Therapy results: SABA offered greater protection than mast cell stabilizers (MCS) (12 studies); MD=6.8 (95 percent CI: 4.5, 9.2) but combining them offered no additional benefit; SABA versus MCS plus SABA (5 studies) MD=1.3 (95 percent CI: -6.3, 8.9). Leukotriene receptor antagonists (LTRA), MCS, ipratropium bromide, and interval warmup routines provided statistically significant attenuation of EIA when compared with placebo; inhaled corticosteroids (ICS) and other warmup routines did not. Single-dose intervention versus placebo results are: LTRA (9 studies) MD=8.9 (95 percent CI: 6.9, 11.0); MCS (nedocromil sodium) (17 studies) MD=15.6 (95 percent CI: 13.2, 18.2); interval warmup versus no warmup (4 studies) MD=10.6 (95 percent CI: 6.5, 14.7); ICS (4 studies) MD=5.0 (95 percent CI: 0.0, 9.9); continuous low intensity warmup versus no warmup (3 studies) MD=12.6 (95 percent CI: -1.5, 26.7); continuous high intensity warmup versus no warmup (2 studies) MD=9.8 (95 percent CI: -6.4, 26.0).

After daily LABA (salmeterol) use for 3 to 4 weeks (4 studies), the percent fall FEV_1 following an ECT at 2 and 4 weeks was greater than at day 1 in the LABA arm indicating that tachyphylaxis to prophylactic LABA use occurred. Daily SABA use for 1 week (1 study) also

indicated development of tachyphylaxis. However, both LABA and SABA continued to have an attenuating effect on EIA.

Conclusions: Given the small number of studies comparing EIB/EIA diagnostic tests, the heterogeneity of the study populations, and the varied study methodologies, there is no clear evidence that any of the index tests are a suitable replacement for a standardized ECT to diagnose EIB/EIA in the general population.

All bronchodilator agents and most anti-inflammatory agents when used as pre-treatment are somewhat effective in attenuating the percent fall FEV_1 associated with EIA. There is evidence that the protective effect of LABA and SABA decreases with the daily use of these drugs. There is no evidence of an attenuating benefit following single-dose pre-treatment with ICS. There is a role for LTRA and MCS; however, the attenuation appears less than with bronchodilator agents. Finally, pre-exercise interval warmup appears to be effective in attenuating the FEV_1 falls associated with EIA.

UPDATE: The following section was added on 3/15/2010:

On February 18, 2010 the Food and Drug Administration issued a drug safety communication requiring changes to use of Long-Acting Beta-Agonists (LABAs) in the treatment of asthma. These changes are based on FDA's analyses of studies showing an increased risk of severe exacerbation of asthma symptoms in some patients using LABAs for the treatment of asthma. The FDA cautioned that LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications and then, LABAs should be used only in combination with these other medications.

The Exercise-Induced Bronchoconstriction and Asthma (EIB/EIA) Evidence Report was conducted prior to the FDA warning and focused on studies that examined whether individuals using LABAs develop a tolerance (tachyphylaxis) to long term regular use of the drugs. The evidence suggests that the protective effect of LABA drugs decrease if they are used daily rather than “as needed” before exercising. These conclusions reflect a different focus than the FDA analysis; however, the conclusions for EIB/EIA do not conflict with the FDA concerns about daily use of LABAs.

Contents

Tables

Figures

Appendixes

Appendixes cited in this report are provided electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/eibeia/eibeia.pdf

Executive Summary

Introduction

Vigorous physical exercise can be followed by *transient* clinical signs and symptoms similar to an asthma attack and are due to post-exercise bronchoconstriction (i.e., a narrowing of the airways). Clinical symptoms include coughing, wheezing, shortness of breath, excessive mucus production, chest tightness, chest pain, or an 'itching or scratching sensation' in the chest. Though it is more common in people with asthma, it also occurs in people without asthma.

For the purposes of this evidence report, we defined exercise-induced bronchoconstriction (EIB) as "the airway obstruction that occurs in association with exercise without regard to the presence of chronic asthma"[1] and we defined exercise-induced asthma (EIA) as "the condition in which exercise induces symptoms of asthma in patients who have asthma."[1] Research is ongoing to determine if the pathogenesis of the phenomenon is the same in non-asthmatics and asthmatics. In this report EIB and EIA were analyzed and discussed separately when the populations and data were specifically identified by authors of the primary studies as one or the other. When it was not clear or studies included patients with and without asthma, we referred to them as EIB/EIA.

The acute bronchoconstriction associated with EIB/EIA peaks rapidly, 3 to 15 minutes after exercise stops, then remits spontaneously within 20 to 60 minutes.[2] It does not cause a persistent deterioration in lung function. Following recovery, a refractory period of 40 minutes to 3 hours has been reported. During this time repeat exercise causes less bronchoconstriction.[3]

Two of the most common pulmonary function measures used to quantify the degree of bronchoconstriction are the forced expiratory volume in 1 second (FEV_1) and the peak expiratory flow (PEF), with FEV_1 considered the more reliable and valid. Both measures will decrease from baseline pre-exercise values in susceptible individuals. It is proposed that the increase in minute ventilation caused by vigorous exercise triggers the airway narrowing.[3,4] Some episodes are severe enough that the person will require an inhaled bronchodilator agent to reverse the bronchoconstriction.

Approximately 20.5 million people in the United States (7 percent) have asthma.[5] Between 60 and 90 percent of people with asthma experience EIA and consider exercise a major trigger of asthma symptoms.[6,7] Prevalence of EIB is lower (6 to 13 percent) in populations with no history of asthma or allergy.[8,9] Among elite athletes the prevalence is reported to range from 10 to 50 percent.[7]

The signs and symptoms of EIB/EIA often go unrecognized or are blamed on lack of conditioning. Some people will avoid exercise and some parents, teachers, and coaches of children with asthma may impose restrictions on which activities will be allowed.[10] With a proper diagnosis and treatment, children and adults have successfully competed at all levels of physical activity.

Key Questions

The objective of this report was to synthesize the evidence for six key questions on diagnostic test accuracy for EIB/EIA and six key questions on therapy for EIB/EIA (five involving pharmaceutical interventions and one on a nonpharmacologic intervention).

D–1. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of a self-reported history/symptoms diary for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–2. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of a methacholine challenge (MCH) for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–3. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of sport/venue specific exercise challenges for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–4. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of eucapnic voluntary hyperpnea (EVH) for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–5. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of a free running asthma screening test (FRAST) for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–6. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of mannitol for diagnosing EIB/EIA compared with a standardized exercise challenge?
T–1. In patients with confirmed EIB/EIA, do patients using short- or long-acting beta-agonists (SABA or LABA) therapy develop tachyphylaxis to treatment and, if so, at what frequency, compared with standard comparator treatments and/or placebo?
T–2. In patients with confirmed EIB/EIA, does pre-exercise treatment with leukotriene receptor antagonist therapy (LTRA) reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?
T–3. In patients with confirmed EIB/EIA, does pre-exercise treatment with inhaled corticosteroid therapy (ICS) reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?
T–4. In patients with confirmed EIB/EIA, does pre-exercise treatment with mast cell stabilizers (sodium cromoglycate or nedocromil; MCS) therapy reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?
T–5. In patients with confirmed EIB/EIA, does pre-exercise treatment with anticholinergic therapy (SAAC) reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?
T–6. In patients with confirmed EIB/EIA, does a refractory period (10 to 15 minute warmup and/or cooldown) reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?

Methods

For questions involving diagnostic test accuracy, we searched MEDLINE®, EMBASE, EBM Reviews - Cochrane Central Register of Controlled Trials, AMED, PsycINFO, PASCAL, CINAHL®, SPORTDiscus with Full Text, Academic Search Elite, Web of Science®, BIOSIS Previews®, PubMed, Scopus®, the Medion Database of Diagnostic Reviews - University of Maastricht, and Proquest Dissertations and Theses. For questions involving EIB/EIA therapy we searched the Cochrane Airways Register. This Register contains references to randomized controlled trials (RCTs) from the Cochrane Central Register of Controlled Trials, MEDLINE®, EMBASE, CINAHL®, AMED, PsycINFO, as well as results from handsearches of respiratory

journals and meeting abstracts. For all questions, we handsearched conference proceedings from key scientific meetings and reference lists of included studies.

Two reviewers independently screened the search results (titles and abstracts) to determine if an article met broad inclusion criteria. The full-text of potentially relevant articles was retrieved and two reviewers independently assessed each study using a standard inclusion/exclusion form. Disagreements were resolved by discussion or through third party adjudication, as needed.

Two reviewers independently assessed the methodological quality of individual diagnostic test accuracy studies using the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) tool[11] and the methodological quality of RCTs in the therapy reviews using the Jadad[12] scale and Schulz's criteria to assess allocation concealment.[13,14]

Two reviewers also independently assessed the strength of evidence for each key question. For the diagnostic test reviews, we used the GRADE system for rating the quality of evidence and strength of recommendations for diagnostic tests.[15] We assessed the strength of the study designs, the quantity and quality of individual studies, the indirectness of evidence, and the consistency and precision of the results. For all studies, the outcomes were measures of test accuracy (i.e., true positive, true negative, false positive, false negative), which are surrogates for patient-important outcomes. For each key question the quality of evidence was graded as high, moderate, low or very low. For therapy reviews, the strength of evidence for the primary outcome (maximum percent fall in FEV_1) was assessed using the EPC approach to grading the strength of a body of evidence.[16] A grade of high, moderate, low, or insufficient was based on four domains: risk of bias, consistency, directness, and precision. Disagreements were resolved by discussion or through third party adjudication, as needed.

Data analysis

The primary outcome used to determine the presence or absence of EIB/EIA was the maximum percent fall in FEV_1 post-exercise challenge calculated using the following formula:

$$\frac{FEV_1 / PEF_{pre-exercise} - \text{minimum } FEV_1 / PEF_{post-exercise}}{FEV_1 / PEF_{pre-exercise}} \times 100$$

The peak expiratory flow (PEF) was used if that was the only pulmonary function measure reported. In the case of missing data, some assumptions and imputations were necessary to transform reported data into the form required for analysis. Data from graphs were extracted using CorelDRAW® 9.0 (Corel Corp., Ottawa, Canada). Means were approximated by medians, and 95 percent empirical intervals were used to calculate approximate standard deviations. In the therapy reviews the majority of studies used a crossover design, therefore, standard errors of mean differences were either computed exactly using individual patient data, or imputed using an estimated within-patient correlation of 0.5. Meta-analyses were conducted using the random effects model where appropriate. The I^2 statistic was used to assess heterogeneity.[17] Planned subgroup analyses included age (children [less than 18 years old] versus adult [18 years and older]), severity of EIB/EIA as defined by the percent fall index on placebo (mild [less than 30 percent] versus moderate-severe [30 percent or more]), and patients with EIB versus EIA. All data pooling was performed using Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).

Therapy reviews

For each study the maximum percent fall in FEV_1 on the placebo ECT was subtracted from the maximum percent fall on the treatment ECT to obtain the difference. For each comparison a mean difference (MD) and 95 percent confidence interval (CI) were calculated using all included studies weighted according to sample size. There were two secondary outcomes of interest: (1) the proportion of people who received complete protection from EIB/EIA with treatment compared with placebo, for which a risk ratio (RR) and 95percent CI were calculated; and (2) the degree of protection received over placebo, known as the "clinical protection index," which was calculated using the following formula:

$$\frac{\text{maximum \% fall } FEV_{1(\text{placebo})} - \text{maximum \% fall } FEV_{1(\text{treatment})}}{\text{maximum \% fall } FEV_{1(\text{placebo})}} \times 100$$

Results – Diagnostic Test Accuracy Review

In addition to a history of symptoms suggesting EIB/EIA following exercise, objective diagnostic testing is necessary to confirm a diagnosis. A fall in the FEV_1 of 10 percent or more after a challenge test is the recommended diagnostic threshold to objectively diagnose EIB/EIA.[18] Testing can be done using either direct or indirect methods. Currently, there is no universally accepted gold standard test to confirm a diagnosis of EIB or EIA. In the absence of a gold standard, a standardized exercise challenge test (ECT) on a treadmill or bicycle ergometer conducted according to the American Thoracic Society guidelines[18] is the best defined reference standard that is available and was used as the reference test in this report. The index tests that were assessed included a self reported history/symptoms diary, one direct challenge, and four indirect challenge tests. Methacholine (MCH) is considered a direct challenge as it acts directly on smooth muscle receptors to cause constriction independent of airway inflammation.[19] The indirect challenges included two alternative exercise protocols (sport/venue-specific and free running asthma screening test [FRAST]), eucapnic voluntary hyperpnea (EVH), and inhaled mannitol. The indirect challenges are thought to cause inflammatory cells to release mediators such as leukotrienes, prostaglandin, and histamine which provoke smooth muscle constriction.[20]

Sensitivity and specificity are two measures of diagnostic test characteristics. Sensitivity is the probability of testing positive if EIB/EIA is really present. Specificity is the probability of testing negative if EIB/EIA is truly absent. As the sensitivity of the test under investigation (index test) increases, the number of persons with EIB/EIA who are missed (false negatives) will decrease. As the specificity of the index test increases, the number of persons without EIB/EIA who are incorrectly classified (false positives) will decrease. To avoid the risk of spectrum bias, diagnostic test accuracy studies should include a broad spectrum of participants who range from high to low likelihood of EIB/EIA.

Twenty-eight studies met the inclusion criteria for the questions relating to diagnostic test accuracy: self-reported history/symptoms diary[21,22] (n=2), MCH[23-37] (n=15), sport or venue specific challenges[34,38-41] (n=5), EVH[34,38,39,42-45] (n=7), FRAST[36,40,46] (n=3), and mannitol[23,47] (n=2).

Table 1 and the following summaries provide an overview of the results of the diagnostic test accuracy review. Sensitivity and specificity are reported for individual studies but data were not pooled due to substantial heterogeneity.

Key Question D–1. Self-Reported History or Symptoms Diary

Many people with potential EIB/EIA present with complaints of symptoms such as shortness of breath, cough, wheeze, and chest pain, associated with exercise[18] and these symptoms have been used to diagnose EIB/EIA. There is a concern that self-report alone leads to an unacceptably high rate of false positive and false negative decisions.[4]

Results. Two studies[21,22] met the inclusion criteria for the diagnostic test accuracy of self-reported history/symptoms diary compared with a standardized ECT.

Frobase et al.[21] matched 20 teenage athletes who answered "yes" to the question "do you experience cough after exercise" to 20 who responded "no." All participants performed a treadmill ECT. The authors used a fall in FEV_1 of 10 percent or more to define a positive ECT. They reported a sensitivity of 89 percent (95 percent CI: 67, 99); a specificity of 86 percent (95 percent CI: 64, 97).

Rupp et al.,[22] gave 166 teenage athletes a questionnaire with two questions relevant to EIB/EIA ("Do you have trouble breathing after running 1 mile and resting?" "Do you have to stop when running for ½ mile?"). Twenty-nine percent were identified as being at risk of EIB/EIA. All took a treadmill ECT. At a threshold of 15 percent or more, the authors reported a sensitivity of 36 percent (95 percent CI: 17, 59); a specificity of 85 percent (95 percent CI: 78, 90).

Methodological quality. Neither study included a representative spectrum of participants or defined their selection criteria and neither study blinded assessors to the results of the other challenge. It is unclear whether the ECTs met the ATS guideline recommendations.[18] Furthermore, the number of "unclear" responses for both studies using the QUADAS tool raises questions regarding bias and generalizability.

Discussion. Despite extensive searching, only two studies addressed this question. The results of one study[21] suggest that exercise-induced cough may be a predictor of EIB/EIA. Self-reported history and symptoms may be a starting point for further investigations but on their own are not sufficient to confirm a diagnosis of EIB/EIA.

Conclusion: There is insufficient evidence to conclude that self-report of symptoms is a reliable diagnostic tool for EIB/EIA. The quality of evidence is classified as "very low." The initial grade based on study design was low and there are serious limitations related to study quality. The diagnostic thresholds differed and the sensitivity estimates are inconsistent and imprecise.

Key Question D–2. Methacholine Challenge

MCH is considered a direct challenge. Once inhaled into the lungs, it acts on smooth muscle acetylcholine receptors causing contraction and airway narrowing.[23] It has been noted that airway responsiveness to pharmacological agents such as MCH is different from hyper-responsiveness to osmotic agents or to hyper-responsiveness following exercise.[18]

The threshold for a positive ECT was a maximum fall in FEV_1 of 10 percent or more from a pre-exercise baseline.[18] The threshold for a positive MCH challenge was a fall in FEV_1 of 20 percent or more at a provocative concentration of less than 8 mg/ml (PC_{20}).[18] We also looked at a threshold PC_{20} of less than 16 mg/ml.

Results. Fifteen studies[23-37] met the inclusion criteria for the diagnostic test accuracy review of a MCH challenge compared with a standardized ECT. The number of participants ranged

from 12 to 375. Considerable heterogeneity was observed across the studies. Overall, 331 participants (57 percent) had a positive ECT and 416 (71 percent) had a positive MCH at the 8 mg/ml threshold. Both sensitivity and specificity ranged from 0 to 100 percent. Using the 16 mg/ml threshold, 420 participants (53 percent) had a positive ECT and 498 (63 percent) had a positive MCH. Sensitivity ranged from 55 to 100 percent and specificity 0 to 100 percent. To explore heterogeneity, we conducted a post hoc subgroup analysis on studies where all participants had mild to moderate stable asthma[24-26,28,29,32,33,35,36] and studies[27,30,34,37] that reported fewer than 50 percent of participants had confirmed asthma. The heterogeneity was reduced somewhat. Among studies in which all participants had asthma, the sensitivity ranged from 66 to 100, specificity 0 to 100 percent; in 4 studies reporting fewer than 50 percent had asthma sensitivity ranged from 0 to 50 percent and specificity 42 to 84 percent.

There was no reduction in heterogeneity when we explored the effects of age (child versus adult), MCH method (5 breath dosimeter versus 2 minute tidal breathing), or ECT parameters (air temperature and humidity, or treadmill versus bicycle ergometer).

Methodological quality. There are several methodological issues in this group of studies. Of concern is the risk of spectrum bias. Most studies did not report how participants were recruited into the study, nor did they describe the inclusion criteria; three studies recruited volunteers.[26,30,34] Blinding of the ECT results to the results of the MCH challenge was not reported. It is unclear whether eight of the ECTs met the ATS guideline recommendations.[18]

Discussion. Across these 15 studies, there was considerable heterogeneity in estimates for sensitivity and specificity although sensitivity estimates varied less when examining patients with a confirmed diagnosis of asthma. Unlike ECTs, a positive airway response to MCH does not imply the presence of inflammatory cells or their mediators that are known to be present in EIB/EIA;[20] therefore, it is not surprising that MCH shows variable sensitivity and specificity to detect EIB/EIA. It has been suggested[18] that a positive MCH test should not be used to infer EIB/EIA and likewise, a negative MCH should not be used to *exclude* EIB/EIA.

Conclusion. Based on the available evidence we cannot conclude that the MCH challenge is a reliable test to diagnose EIB/EIA in those with confirmed asthma or in populations with mixed asthma prevalence. The quality of evidence is classified as “moderate.” The initial grading based on study design was high; however, there are serious limitations to quality of individual studies. Sensitivity estimates are reasonably consistent but are imprecise in the participants with EIA. Specificity estimates are inconsistent and imprecise.

Key Question D–3. Sport or Venue Specific Exercise Challenge

Sport/venue specific challenges are advantageous in that the athlete can exercise in the conditions where they become symptomatic and the tests are reasonably inexpensive. In comparing sport/venue specific challenges with an ECT, coordinating the timing of the two tests and ensuring good quality control on the sport challenges can be problematic. The environmental conditions, level of intensity, and increase in minute ventilation reached during both challenges may be hard to match.

The threshold for a positive ECT or a sport specific challenge was a maximum fall in FEV_1 of 10 percent or more from a pre-exercise baseline.[18]

Results. Five studies[34,38-41] met inclusion criteria for the diagnostic test accuracy review of sport or venue specific exercise challenges compared with a standardized ECT. Three focused on swimming challenges[34,38,40] and two assessed cold weather sport challenges.[39,41] Rundell et al.[41]

only included athletes who tested positive on a sport specific challenge. The sensitivity of the swimming challenge tests ranged from 0 to 50 percent; specificity from 83 to 100 percent. In total 11 (19 percent) participants were positive on the ECT and 5 (9 percent) were positive on the swim challenge. In the two studies involving winter athletes, Dickensen et al.[39] had no true positives but a specificity of 79 percent, and Rundell et al.[41] sensitivity of 100 percent but had no true negatives and a specificity of 0 percent.

Methodological quality. In these five studies there are some methodological weaknesses. None of the studies had a representative patient spectrum which suggests the possibility of spectrum bias. Blinding of ECT results to the results of the index test was not reported. It is unclear whether two of the ECTs met the ATS guideline recommendations.[18]

Discussion. These studies compared challenges in the specific sport the athletes practiced (e.g., biathlon) or at the venue of activity (e.g., skating arena, swimming pool) to a laboratory ECT. The estimates of sensitivity and specificity both, ranged from 0 to 100 percent. Sport specific challenges are one of the recommended challenges for diagnosing EIB/EIA in elite athletes;[34] however, in total only seven athletes were positive in their own field of competition while 16 were positive on a standardized ECT. It is not clear why this occurred, although it is possible that the level of minute ventilation and differences in environmental conditions played a role.

Conclusion. Sport specific challenges may be useful in identifying athletes who do *not* have EIB/EIA but other testing such as a standardized ECT may also be required. The quality of evidence is classified as "low." The initial grading based on study design was high; however, there are serious limitations related to study quality. The sensitivity estimates are inconsistent and imprecise. Specificity estimates are also inconsistent and imprecise.

Key Question D–4. Eucapnic Voluntary Hyperpnea

Eucapnic voluntary hyperpnea (EVH) is a test based on the premise that the increased minute ventilation with exercise is responsible for bronchoconstriction in susceptible subjects.[48] The EVH challenge requires the person to increase their minute ventilation up to 80-85 percent of the maximum minute ventilation for 5-6 minutes, which approximates the minute ventilation obtained during vigorous exercise. EVH was developed as a surrogate for exercise to identify EIB[49] and currently, it is the challenge recommended by the International Olympic Committee Medical Commission to identify EIB/EIA among Olympic athletes.[19]

The threshold for a positive ECT or EVH challenge was a maximum fall in FEV_1 of 10 percent or more from a pre-exercise baseline.[18]

Results. Seven studies[34,38,39,42-45] met inclusion criteria for the diagnostic test accuracy review of EVH compared with a standardized ECT. The number of participants ranged from 10 to 33. Substantial heterogeneity was identified. Forty-two (30 percent) participants had a positive ECT and 74 (54 percent) had a positive EVH. Sensitivity estimates ranged from 25 to 90 percent and specificity from 0 to 71. A post hoc subgroup analysis of studies in which participants did not have known EIB/EIA[34,38,39,42] explained some of the heterogeneity. In this population, the sensitivity ranged from 25 to 75 percent and specificity from 29 to 71 percent. Among studies in which all participants had EIB/EIA,[42-45] the sensitivity of EVH was high, ranging from 71 to 90 percent; however, one study had no true positive cases[42] and three had no true negative cases.

Methodological quality. As a group, there are methodological weaknesses that limit the interpretation and generalizability of the results. Of greatest concern is the risk of spectrum bias

in all studies. Either the participants recruited into the studies were volunteers,[34,38,39,42,44] or the recruitment source and methods were not reported.[43,45] In some studies all participants had a history of EIB/EIA[43-45] and therefore are not representative of the spectrum of patients who might be tested for EIB/EIA. Blinding of the ECT results to the results of the EVH challenge was not reported. It is unclear whether the ECTs met the ATS guideline recommendations.[18]

Discussion. Overall, both the sensitivity and specificity of EVH compared to an ECT showed substantial heterogeneity and no trend was observed. It is unclear whether an EVH challenge is identifying the same people that experience a fall in FEV_1 of 10 percent or more on an ECT, particularly in a population of athletes with an unclear history of asthma. The EVH challenge resulted in a higher proportion of false positives (FP) (i.e., negative on the ECT but positive on EVH) among participants with no or unknown history of EIB/EIA. The proportion of FP ranged from 25 to 71 percent. The participants included both elite athletes (n=63) and those with unknown activity levels (n=20). Based on the available evidence, it is unclear if the EVH challenge is more sensitive to EIB/EIA, or if the mechanism that triggers the bronchoconstriction is different from that for the ECT, or if level of minute ventilation achieved on an ECT according to ATS recommendations is less than the level achieved in an EVH challenge particularly in athletes. Among participants with a history of EIB/EIA, the proportion of FPs ranged from 0 to 5 percent in participants with unknown activity levels. Among athletes, the proportion with a FP result was 27 percent. Further research is needed to determine if the EVH challenge would be an appropriate add-on test to an ECT in athletes with symptoms of EIB/EIA.

Conclusion. Based on the available data, we cannot conclude that an EVH challenge is a reliable diagnostic test for EIB/EIA. The quality of evidence is classified as "low." The initial grading based on study design was high; however, there are serious limitations related to study quality. Furthermore, the sensitivity and specificity estimates are inconsistent and imprecise.

Key Question D–5. Free Running Asthma Screening Test (FRAST)

Free running has often been used in screening large groups for EIB/EIA because the test is relatively easy to perform, requires limited equipment, and multiple subjects can be tested at the same time.[48] The threshold for a positive ECT or FRAST was a maximum fall in FEV_1 of 10 percent or more from a pre-exercise baseline.[18]

Results. Three studies[36,40,46] met inclusion criteria for the diagnostic test accuracy review of FRAST compared with a standardized ECT. Participants were children under 15 years, and all free running tests took place indoors. In two studies[36,40] the threshold for a positive FRAST was a fall in FEV_1 of 10 percent or more. In these 34 participants, 13 (38 percent) had a positive ECT and 18 (41 percent) had a positive FRAST. The sensitivities were 60 and 67 percent; specificities were 47 and 67 percent. The remaining study[46] used a threshold of a fall in FEV_1 of 16.5 percent or more for the FRAST and 20 percent or more for the ECT. Based on these thresholds the sensitivity was 53 percent (95 percent CI: 34, 72); specificity was 100 percent (94 percent CI: 88, 100).

Methodological quality. Overall, there were concerns about the methodological quality of the studies. Generalizing the results to a target population of people with suspected EIB/EIA may be limited as none of the studies had representative spectrum of participants. Blinding of results of the ECT to the results of the FRAST was not reported. It is unclear whether two of the ECTs met the ATS guideline recommendations.[18]

Discussion. Sensitivity and specificity of FRAST were modest (60 to 67 percent and 47 to 67 percent, respectively). While the FRAST may be easy to perform, there is insufficient evidence to conclude that it accurately identifies people with EIB/EIA compared with a standardized ECT. Furthermore, in a FRAST challenge there is an overall lack of control in terms of exercise intensity and therefore stimulus (i.e., minute ventilation).

Conclusion. There is insufficient evidence to conclude that FRAST is a reliable diagnostic test for EIB/EIA. The quality of evidence is classified as "very low." The initial grading based on study design was moderate; however, there are serious limitations related to study quality. The sensitivity and specificity estimates are consistent but imprecise.

Key Questions D–6. Mannitol Challenge

Recently, a mannitol provocation test has been developed to examine airway hyper-responsiveness. Like exercise, mannitol is thought to cause airway narrowing indirectly through increasing the osmolarity of the airway surface, leading to the release of endogenous mediators such as prostaglandin, leukotrienes and histamine, and resulting in smooth muscle contraction.[50,51] Mannitol has the advantage that it can be performed with minimal equipment (i.e., a metered-dose inhaler and spirometer).

The threshold for a positive ECT was a maximum fall in FEV_1 of 10 percent or more. The threshold for a positive mannitol challenge was a 15 percent drop in FEV_1 at less than 635mg or a drop of 10 percent between consecutive doses.[23]

Results. Three studies[23,47,52] met the inclusion criteria for the diagnostic test accuracy review of mannitol compared with a standardized ECT. All participants in Brannan et al.[47] and Kersten et al.[52] had diagnosed asthma. In these 58 participants, 39 (67 percent) had a positive ECT test, 35 (67 percent) had a positive mannitol challenge. The sensitivity was 69 and 96 percent, respectively. Specificity was 78 percent in the Kersten et al.[52] study. Anderson et al.[23] included those with suspected but not confirmed asthma and reported a sensitivity of 58 percent (95 percent CI: 50, 66) and a specificity of 65 percent (95 percent CI: 58, 72).

Methodological quality. Concern regarding the risk of spectrum bias in the studies by Brannan et al.[47] and Kersten et al. limits the conclusions that can be drawn.[52] Participants were volunteers who had a history of EIA and are not representative of the spectrum of patients who might be tested for EIB/EIA. Blinding of the results of the ECT and the index test was not reported. All three of the ECTs met the ATS guideline recommendations.[18]

Discussion. Both mannitol and ECT are considered indirect tests, acting through a similar mechanism of increasing osmolarity of the airway surface. The advantage of mannitol is that exercise is not a requirement, and the test can be conducted in a physician's office with minimal equipment. Among adults and children with a history of EIA or suspected asthma, the diagnostic test characteristics for mannitol compared to an ECT hold promise. Its role as a screening or diagnostic tool requires further study.

Conclusion. Based on these data, it is difficult to conclude that the mannitol provocation test is a reliable diagnostic test for EIB/EIA. The quality of evidence is classified as "moderate." The initial grading based on study design was high; however, there are concerns regarding the limitations related to study quality. The sensitivity and specificity estimates are reasonably consistent but are imprecise.

Results – Therapy Reviews

The primary objective of therapy is to prevent EIB/EIA from occurring or, short of that, to at least attenuate the degree of bronchoconstriction. Pharmacologic effect is assessed by taking a single dose of an inhaled agent prior to an ECT that meets intensity and ventilation standards. FEV_1 or PEF is measured immediately following the challenge and at 5 minute intervals until lung function begins to improve. The maximum fall in FEV_1 is expressed as a percent of the baseline measure taken immediately prior to the ECT. The greater the percent fall, the worse the EIB/EIA or, conversely, the less the percent fall the more effective the therapy. This report conducted systematic reviews of randomized controlled trials (RCTs) involving four categories of prophylactic agents compared with a placebo: inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRA), mast-cell stabilizers (MCS), and short-acting anticholinergics (SAAC). We conducted two additional reviews. The first was to determine if using short- or long-acting beta agonists (SABA or LABA) on a daily basis caused people to develop a tolerance, or tachyphylaxis, to these agents thus reducing the prophylactic effect on EIB/EIA. If the post-exercise drop in FEV_1 increases after prolonged use of SABA or LABA, it is an indication of tachyphylaxis. The second review investigated whether engaging in a specific warmup routine prior to an ECT caused a refractory period during which time the EIB/EIA response was prevented or attenuated on a subsequent ECT.

The primary outcome for these six reviews was the mean difference (MD) between the mean maximum percent fall in FEV_1 on drug or warmup and the mean maximum percent fall in FEV_1 with placebo or no warmup. In this executive summary, we report the absolute MD in order to phrase the results using positive numbers. In the forest plots in the main report, a negative MD that falls to the left of the null line indicates the drug performed better than the placebo and, by extension, a larger difference indicates a greater drug effect. The 95 percent CIs relate to whether or not the result represents a statistically significant improvement.

Overall, 109 studies were included in the therapy reviews. The included studies addressed the following research questions: tachyphylaxis to SABA and LABA[53-63] (n=11), LTRA[44,64-71] (n=9), ICS[72-75] (n=4), MCS (n=3 Cochrane reviews and publications[76-78]), SAAC[79-96] (n=18), and a refractory period[97-103] (n=7).

Table 2 and the following summaries provide an overview of the results. The pharmacological treatments were further divided into *bronchodilating* and *anti-inflammatory* agents.

Pharmacological Interventions: Bronchodilating Agents

T–1. Tachyphylaxis to SABA or LABA Therapy

β_2-Receptors on the airway smooth muscle are responsible for bronchodilation; beta-agonist agents attach to these receptors and are effective bronchodilators and improve breathing. SABA agents have been the mainstay of EIB/EIA treatment for many years. With the development and availability of LABA agents, more research has been applied to the effectiveness of these agents in preventing EIB/EIA. It has been reported in the literature that some people develop a tolerance

(tachyphylaxis) to long term regular use of beta-agonist drugs and they lose some of their effectiveness and protective effect.[57,59]

Seven studies met inclusion criteria to address the question of whether people with EIB/EIA develop tachyphylaxis to LABA agents[53-61] and two met the inclusion criteria for SABA agents.[62,63] Overall, the quality of the trials was high. All were randomized, double-blind trials that described the withdrawals and dropouts. Five described an adequate process to ensure double-blinding.

SABA. Data from the two SABA crossover studies could not be combined and are therefore described individually. Both studies involved asthmatics who took 1 week of regular (four times per day) SABA or placebo prior to exercise challenges and measured the baseline FEV_1 at the end of the treatment weeks. In one study[63] there was a statistically significant 230 ml difference (p=0.02) in the measure of FEV_1 after the treatment weeks that favored placebo. In the second study,[62] there was no significant difference between the mean FEV_1 after the placebo week compared with the salbutamol week (2.8L versus 2.8L).

Only the study by Inman and O'Byrne[63] assessed prophylaxis. When the 10 adults took a single dose of placebo prior to an ECT on day 8, the mean fall in FEV_1 was positive for EIA in both groups; however, the fall was slightly greater after the SABA week (29.4 ± 4.7 percent versus 24.9 ± 4.4; p=0.12). On day 9 following pre-treatment with a SABA, all received total protection from EIA; however, the fall in FEV_1 was greater after the SABA week (5.1 ± 2.0 percent versus 1.1 ± 0.8; p=0.05) and remained lower throughout the recovery period. Adverse events were not reported. Hancox[62] randomized 8 women with EIA and following a week of study drug performed an ECT with no pretreatment but gave SABA 5, 10, and 15 minutes post ECT. The fall in FEV_1 was greater in the SABA treated group (p=0.001).

LABA. Four crossover trials[55,57-59] randomized groups to 3 to 4 weeks of salmeterol[55,57] once a day,[59] or every other day[58] or to a matching placebo. The average fall in FEV_1 after the first ECT on day 1 was 3.7 percent in the LABA arms compared with 26.9 percent in the placebo arms. The absolute MD was 25.1 percent (95 percent CI: 18.0, 32.3) In the individual studies the percent fall in FEV_1 following an ECT at both 2 weeks and 4 weeks was of a greater magnitude in the LABA arms than at day 1, indicating a greater degree of EIA and less protection from salmeterol. The fall in FEV_1 in the placebo arms remained unchanged or showed a small decrease. After 4 weeks of daily LABA use, the average fall in FEV_1 after an ECT (3 studies) increased to 11.4 percent in the LABA arms compared with a decrease to 21.3 percent in the placebo arms. The pooled MD was 10.5 percent (95 percent CI: 14.7, 6.4. Three headaches were attributed to salmeterol; one exacerbation and one complaint of chest tightness were attributed to placebo.

The study by Garcia et al.[54] compared daily formoterol with placebo and also concluded that twice daily LABA over 4 weeks caused a significant reduction in bronchoprotection against EIA. Though the LABA was still effective, tachyphylaxis was evident by day 14. Adverse events were not reported.

Two studies compared regular use of salmeterol versus a LTRA (montelukast) once in the evening for 8 weeks.[53,60] Both drugs attenuated the EIA response after 3 days of treatment to a similar degree. The mean fall in FEV_1 on LABA was 19.8 percent compared with 18.2 percent on LTRA (MD=1.01; 95 percent CI: -2.2, 4.2). Montelukast maintained its effectiveness at 4 and 8 weeks compared with a slight decrease in effect with regular use of salmeterol. At 8 weeks the mean fall in FEV_1 on LABA increased to 23.0 percent compared with a slight decrease to 17.1 percent on LTRA. The pooled MD was 5.4 (95 percent CI: 2.2, 8.7). This evidence, although

indirect, provides additional support for the concept of tachyphylaxis following regular use of LABA agents in patients with EIA. Adverse events were infrequent, mild and occurred more or less equally between therapies.

Discussion. Based on the results of one study,[63] SABA agents were found to have a prophylactic effect on EIA. The day 1 data from the LABA tachyphylaxis review also show that LABA is effective for attenuating the drop in FEV_1 post exercise. However, the evidence indicates tachyphylaxis is associated with the regular use of both SABA and LABA agents. The results of this review demonstrated that the percent fall in FEV_1 following an ECT after 1 to 4 weeks of use was greater (i.e., drugs were becoming less effective) in the SABA and LABA arms than in the placebo arms. Notwithstanding the tachyphylaxis, a prophylactic effect for SABA and LABA was still observed.

Conclusion. Given the consistency of results, the magnitude of effect and concordance with clinical consensus, the evidence indicates that prophylactic use of SABA and LABA agents is safe and effective for episodic prophylaxis of EIA. The evidence suggests that tachyphylaxis develops if these agents are used daily. The body of evidence comparing SABA/LABA to placebo was graded as "moderate"; evidence comparing LABA to LTRA was graded as "low."

Pharmacological Interventions: Anti-Inflammatory Agents

T–2. Leukotriene Receptor Antagonist Therapy

Leukotrienes are produced by the cysteinyl leukotriene pathway and are implicated in both bronchoconstriction and in the inflammatory cascade leading to worsening asthma. LTRAs are relatively new agents available for the management of chronic and acute asthma which block this pathway.

Nine crossover trials[44,64-71] met the inclusion criteria for the single prophylactic use of LTRA compared with placebo in the pre-treatment of EIA. Overall, the methodological quality of the trials was good. All were randomized, eight were double-blind trials and six described an adequate process to ensure double-blinding. Seven described the withdrawals and dropouts; however, none described the method of randomization and only one had adequate allocation concealment. All trials recruited people with asthma and confirmed EIA and all recorded the mean fall in FEV_1 up to 2 hours after drug administration. The pooled results showed that LTRA was more effective than placebo in preventing EIA. The average fall in FEV_1 in the LTRA arms after the first ECT ranged from 7.6 to 13.3 percent (average 10.9) compared with 15.0 to 23.2 percent (average 18.5) on the placebo challenges. The absolute MD was 8.3 percent (95 percent CI: 6.9, 11.0; I^2=65 percent) and represented clinical protection of approximately 45 percent over placebo. Three trials[68,70,71] recorded the mean maximum fall in FEV_1 24 hours after drug administration. The average fall in the placebo arms was 13.8 percent (range 10.7 to 16.9) compared with 8.7 percent (range 8.3 to 10) in the LTRA arms. The pooled results showed that LTRA remained more effective than placebo in preventing EIA (MD=4.9; 95 percent CI: 1.8 to 8.0; I^2=76 percent). Adverse events were infrequent, mild and occurred more or less equally between LTRA and placebo groups.

Discussion. We identified nine trials of LTRA compared with placebo in the pre-treatment of EIA. The methodological quality of the studies was high and the pooled results demonstrated a consistent benefit associated with prophylactic use. LTRAs reduced the maximum percent fall in

FEV_1 at the earliest measurement by approximately nine percent compared with placebo (Table 2).

Conclusion. From the available evidence, it appears that LTRAs are effective and safe as pre-exercise treatment for patients with mild to moderate stable asthma and EIA. The strength of the body of evidence is "moderate."

T–3. Inhaled Corticosteroid Therapy

The main inhaled anti-inflammatory agents used for chronic and acute asthma are ICS agents. The search and selection methods employed for this review identified trials involving single prophylactic ICS use compared with placebo in the pre-treatment of EIA.

Four crossover trials[72-75] met the inclusion criteria. Overall the quality of the trials was good. All were randomized and double-blind; two described an adequate process to ensure double-blinding. All described the withdrawals and dropouts; however, none described the method of randomization and one had inadequate allocation concealment. All trials recruited people with stable asthma and confirmed EIA. The pooled results showed no significant difference between ICS and placebo (absolute MD=5.0 percent; 95 percent CI 0.0, 10.0; I^2=0 percent). None of the studies reported adverse events.

Discussion. The pooled results failed to produce a statistically significant or clinically important reduction in the percent fall in FEV_1 compared with placebo.

Conclusion. From the available evidence, we cannot concude that a pre-exercise single-dose of an ICS agent will attenuate EIA. The strength of the body of evidence is "moderate."

T–4. Mast Cell Stabilizers

Three systematic reviews were identifed that synthesized the evidence for MCS. One review compared nedocromil sodium (NCS) versus placebo for preventing EIA[76,104] and one compared NCS versus sodium cromoglycate (SCG).[77] The third review[78] compared the effects of a prophylactic dose of either NCS or SCG (collectively called MCS) to that of atropine, ipratropium or oxitropium bromide (collectively called SAAC agents) and to SABA. The review also compared the effects of a combination of a SABA plus a MCS to a SABA alone. Our search strategy located no additional RCTs that would add to these reviews. In the three reviews, all trials recruited people with stable asthma and confirmed EIA.

Twenty-one RCTs were included in the NCS versus placebo review.[76,104] NCS provided a statistically and clinically significant attenuation of EIA. The average fall in FEV_1/PEF was 15.2 percent (range 10.0 to 29.8) in the NCS arms compared with 31.5 percent (range 17.5 to 47.2) in the placebo arms (absolute MD=15.6 percent; 95 percent CI: 13.2, 18.1; I^2=20 percent). This represents a clinical protection index of approximately 51 percent over placebo. In those that had more severe EIA (i.e., a percent fall index 30 percent or more), the effect of NCS appeared more pronounced (absolute MD=21.4 percent; 95 percent CI: 25.5, 17.2).

There were nine RCTs included in the NCS versus SCG review.[77] No significant differences between NCS and SCG were identified (absolute MD=0.88; CI: -4.5, 2.7; $I^{2=}$0 percent).

There were 24 RCTs included in the review comparing MCS to other agents. Overall, the maximum fall on MCS was reduced to 7.1 percent compared with 13.8 percent on SAAC agents (MD=6.7 percent; 95 percent CI: 3.3, 10.0; I^2=0 percent). When compared with SABA, MCS were not as effective at preventing EIA. The mean percent fall in FEV_1 using MCS was 11.2

percent compared with 4.3 percent on SABA (MD=6.8 percent; 95 percent CI: 4.5, 9.2; I^2=0 percent). Combining MCS with a SABA did not produce significant advantages to pulmonary function over SABA alone (MD=1.8 percent; 95 percent CI: -1.1, 4.6; I^2=0 percent). Few trials reported adverse events due to MCS; those that did reported bad taste, throat irritation and cough.

Discussion. MCS stabilize the mast cell membranes and prevent the release of inflammatory mediators; they are used as weak anti-inflammatory agents in mild to moderate chronic asthma. Examining existing Cochrane reviews, this report highlights the efficacy (approximately 51 percent improvement in the post-exercise FEV_1 compared with placebo) for NCS. An analysis failed to demonstrate a difference between NCS and SCG and further comparative analyses suggest that MCS are more effective than SAAC agents but less effective than SABA agents (Table 2).

Conclusion. From the available evidence, it appears that MCS agents are effective and safe as pre-exercise treatment for patients with stable asthma and EIA. No significant differences were identified between NCS and SCG on pulmonary function or degree of protection afforded to patients. MCS agents were somewhat more effective than SAAC agents but not as effective as SABA agents. The combination of SABA and MCS agents did not provide significant advantages over a SABA alone. The strength of the body of evidence is "moderate."

T–5. Anticholinergic Therapy

SAAC agents are used in respiratory conditions to decrease mucus production and as weak bronchodilators. The original anticholinergic agent used in asthma was atropine; however, ipratropium bromide (IB) is now the most commonly used agent in this class. Long-acting anticholinergic agents such as titropium bromide are also now available. The search and selection methods employed for this review trials involving single prophylactic SAAC use compared with placebo in the pre-treatment of EIA.

Eighteen crossover trials[79-96] met the inclusion criteria. Overall, the methodological quality was low. Though all were randomized, seven were not double-blind trials and only one described an adequate process to ensure double-blinding. Seventeen trials described the withdrawals and dropouts; however, none described the method of randomization and all had unclear allocation concealment.

All trials recruited people with stable asthma and confirmed EIA. The mean fall in FEV_1/PEF on the placebo challenges ranged from 14 to 41 percent (average 32). Seven of the placebo groups[79,83,85,88,90,93,96] had a mean fall in FEV_1/PEF greater than 30 percent indicating moderate to severe EIA. The average fall in FEV_1/PEF in the SAAC arms ranged from 10 to 33 percent (average 21). The pooled results showed that IB was more effective than placebo in preventing EIA (absolute MD=8.8 percent; 95 percent CI: 5.0, 14.6; I^2=76 percent). Four trials compared atropine to placebo.[80,84,86,91] The pooled results showed that atropine was more effective than placebo in preventing EIA (absolute MD=16.0; 95 percent CI: 10.2, 21.7; I^2=0 percent). Two trials compared oxitropium bromide to placebo.[88,89] The pooled results showed that oxitropium bromide was more effective than placebo in preventing EIA (absolute MD=13.8; 95 percent CI: 6.0, 21.6; I^2=0 percent). Few trials reported adverse events; those that did reported dry mouth or thirst, bitter taste, and slight tremor.

Discussion. The pooled results demonstrated a modest but consistent benefit associated with the pre-exercise use of IB in EIA. IB reduced airway narrowing at the earliest measurement by

34 percent over placebo; however, the results should be viewed cautiously due to the presence of heterogeneity. Complete protection was achieved 4.5 times more often with IB than placebo.

Conclusion. The evidence suggests that when used as a pre-treatment, SAAC agents are effective and safe for patients with EIA and can offer a clinically relevant protective effect to some people. The strength of the body of evidence is "moderate."

Nonpharmacologic Interventions

T–6. Refractory Period (10 to 15 Minute Warmup and/or Cooldown)

As an alternative, or in addition to using medications to attenuate EIB/EIA, many athletes, trainers and researchers advocate specific warmup routines as a method to trigger a refractory period. A refractory period is the time after the warmup routine during which further vigorous exercise will evoke significantly less severe or no EIB/EIA.

Seven trials[97-103] met the inclusion criteria. Overall, the methodological quality was low. All were randomized, but none were double-blind trials. Six described the withdrawals and dropouts; however, none described the method of randomization and all had unclear allocation concealment. Six of the seven trials reported participants had stable asthma and confirmed EIA.

The effect of a warmup routine on EIA prior to a standard exercise challenge was examined for the following subgroups.

Interval protocol. Four trials compared an interval warmup to no warmup[97,99,100,103] prior to an ECT. The MD in the percent fall FEV_1 on the ECT ranged from an improvement of 4.8 to 16.1 percent over the fall after no warmup. The pooled results showed that a series of short intense sprints attenuated the EIA response by a mean of 10.6 percent (95 percent CI: 6.5, 14.7; I^2=15 percent).

Continuous low intensity protocol. Three trials compared a continuous low intensity warmup that ranged from 3 minutes[101] to 30 minutes[102] to no warmup prior to an ECT. The mean difference in the percent fall in FEV_1 on the ECT ranged from an improvement of 0 to 20.6 percent over the fall after no warmup. The pooled results failed to demonstrate statistically significant evidence that the low intensity warmup attenuated the EIA response (absolute MD=12.6 percent; 95 percent CI: -1.5, 26.7; I^2=90 percent).

Continuous high intensity protocol. Two trials compared a continuous high intensity warmup that was identical to the ECT with no warmup prior to the ECT.[102,103] The mean difference in the maximum percent fall in FEV_1 on the ECT ranged from an improvement of 1.0 to 17.6 percent over the fall after no warmup. The pooled results failed to demonstrate statistically significant evidence that a continuous high intensity warmup attenuated the EIA response. (absolute MD=9.8 percent; 95 percent CI: -6.4, 26.0; I^2=89 percent).

Discussion. Seven RCTs compared either different warmup routines with each other or with no warmup prior to an ECT. The evidence suggests that compared with no warmup, pre-treatment of EIA with interval warmup exercise offers a statistically significant and homogeneous attenuating benefit of approximately 11 percent improvement in the percent fall FEV_1 index (Table 2). For both high and low intensity continuous warmup protocols, the evidence is less clear. Combinations of interval and continuous warmup protocols compared within one study identified no differences and all protocols provided similar protection against EIA in the 10 to 11 percent range.

Conclusion. From the available evidence, it appears that certain warmup protocols are effective in reducing the degree of airway obstruction associated with EIA. Combination warmups show promise; however, it is unclear whether continuous warmups are effective in this condition. The strength of the body of evidence is "low."

Gaps in Evidence and Recommendations for Future Research

Methodological Limitations of the Reviews

This review has methodological and logistic limitations. Some of the important limitations are listed below.

Diagnostic test accuracy reviews. Since there is no universally accepted gold standard to diagnose EIB/EIA, we used the standardized ECT based on ATS guidelines as our reference standard. Not all studies performed the ECT according to the ATS guidelines, however, and the variations in ECT protocol among studies may have affected the pulmonary response to the challenge and underestimated the number of positive results. Specifically, there were variations in environmental conditions (percent humidity and temperature of inspired air); restrictions on nose breathing; speed, grade, intensity and duration of the challenge; and target heart rate and minute ventilation achieved during the ECT. All of these have the potential to influence the stimulus for triggering EIB/EIA. These variations may have contributed to the heterogeneity in sensitivity and specificity observed with all the index tests.

Another concern is that many studies suffered from a potential spectrum bias. Ideally, studies should have a sample of participants who are representative of the population being examined for EIB/EIA. That is, studies should have sufficient subjects that span the range from high to low likelihood of EIB/EIA. In this review, many studies purposely recruited volunteers who either had known EIB/EIA, or definitely did not have it. In several studies no information on baseline likelihood was reported. The lack of a representative patient spectrum limits the generalizability of the results to a target population of people with suspected EIB/EIA and makes estimates of sensitivity and specificity unreliable.

A further limitation is that not all potentially relevant studies reported sufficient data to generate a 2x2 table comparing the reference standard result with an index test result based on one or more diagnostic thresholds.

Finally, poor reporting of study methods, challenge criteria, or participant characteristics meant we were not able to perform important subgroup analyses to provide more useful evidence summaries.

Therapy reviews. A double-blind RCT is considered the highest quality study design for assessing drug therapy. A short-coming of many of the included trials was a lack of disclosure on the methods used to generate and conceal the randomization code from investigators and participants as well as the adequacy of the blinding process.

Concerns regarding crossover trials, even though randomized, center on three factors: drug carryover effects, period effects, and statistical issues. Ideally, results should be reported for each treatment period and the test sequence reported so analyses can confirm the presence or absence of a carryover or period effect. No study reported data in such a manner and all merged the results from the treatment and placebo periods as though it were a parallel study.

Studies did not always provide sufficient quantitative data (e.g., measures of variance, mean endpoint estimates, statistical test results) needed to pool the individual trial results and to judge the treatment-related between group outcome differences.

In studies assessing the effect of a refractory period, the warmup protocols were not standardized. We categorized the warmup interventions into three groups, but still within each group the warmup approaches varied from each other.

Studies varied in the presentation of FEV_1 and PEF data. Our primary outcome was the maximum percent fall in FEV_1 from baseline. When possible we transformed data to this measure. The ATS convention is to accept a 10 percent maximum fall in FEV_1 following ECT as the diagnostic cutpoint for EIB/EIA and the majority of studies used this. However, other cutpoints were used and it was not always possible to obtain data at the 10 percent level. The review provided data on 15 and 20 percent cutpoints when available. While outcome reporting mainly included detailed pulmonary function measures, data on the proportion obtaining clinical and complete protection were not always reported nor was it standardized (Table 2).

Side effect profiles were also poorly reported. While side effects were likely uncommon, better reporting and the use of patient treatment preference may have provided more robust assessments of the effectiveness of various treatment options. Finally, most studies relied exclusively on pulmonary function outcomes to assess effectiveness; symptom control and exercise performance data were not available.

Recommendations for Future Research

Efforts are needed to improve the overall quality of reporting of primary studies of diagnostic test accuracy. The STARD checklist[105] details 25 items that address the level of detail that should be specified within such studies including descriptions of participants, tests methods, statistical methods, and results. This could be considered as a guide for authors reporting studies that evaluate diagnostic tests and for journals that publish EIB/EIA-related research.

Studies designed to more carefully examine the methodology of the standard ATS ECT test are needed. Specifically, guidelines state that the inspired air temperature must be less than 25^{o}C, and less than 50 percent relative humidity. Studies have used inspired air as cold as -18^{o}C and many have used medical compressed air, which has a relative humidity of 0 percent as the air leaves the tank. Colder, drier air would result in the greatest increase in osmolarity of the airway surface and thus most likely cause EIB/EIA. Additional studies are needed to more thoroughly examine how inspired air affects EIB/EIA so that a more standardized ECT guideline can be developed.

Future purposely designed studies to compare the diagnostic characteristics of different diagnostic methods are needed. New tests such as mannitol are encouraging; however, currently there are insufficient data to allow for a strong recommendation of this test. Particular attention in future studies must be given to including a representative sample of participants with suspected EIB/EIA. Studies that prospectively recruit participants and blind the reference standard results to those who interpret the index test results are needed.

To determine if the response to diagnostic tests differs in those with EIB versus EIA, those with atopy or no atopy, or other potentially defining characteristics, appropriate populations need to be included, adequate baseline data reported, and comparative analyses by the characteristics of interest performed and reported.

With regard to the systematic review of therapy for EIA, there are several issues with respect to methodological quality, populations, interventions, outcome assessments, and controls that require discussion.

Efforts are needed to improve the quality of reporting primary studies (i.e., randomized controlled trials). The CONSORT Statement[106] could be considered as a guide for authors reporting trials and journals that publish EIB/EIA-related research. Most trials in this review used a crossover design. Concerns regarding crossover trials center on three factors: drug carryover effects, period effects, and statistical issues. Data should be reported in a manner that allows analyses to confirm the presence or absence of a carryover effect. Future studies should focus on complete reporting of results by period and sequence to assure readers that these concerns have been accounted for.

Population: The populations involved in the therapy trials all had stable asthma and confirmed EIA. Athletic status was not reported. This finding, coupled with the small number of studies investigating some interventions, precluded more detailed subgroup analysis of the issue of EIB/EIA in elite athletes. Additional investigations of treatment effects in patient subgroups defined by asthma severity, age, and activity level are clearly indicated.

More trials in clinically homogenous groups of patients with EIB and patients with EIA are needed to better explore and characterize differences in the efficacy of interventions between these two conditions.

Intervention: The nonpharmacologic interventions were not standardized. Although the warmup interventions were divided into similar groups, each warmup approach varied from the others. Future research exploring different standardized warmup approaches is clearly indicated.

Control: Many of the patients in the pharmacological studies were administered placebo agents as the control treatment. These agents were often similar in appearance or delivered in similar appearing devices (inhaler agents) to the active treatment; however, it may have been possible for patients to detect differences among treatments, especially the bronchodilators such as SABA, LABA and SAAC agents. It is impossible to determine how frequently this occurred since most studies did not report the patient's perception of treatment received. In addition, it was not possible to blind the participants to the warmup programs in the refractory studies. When the participant cannot be blinded, it is particularly important that the outcome assessor be blinded to all information that could bias the outcome measure or assessment (e.g., other test results, intervention given, challenge performed).

Outcome: The pulmonary function outcomes reported varied and studies used different diagnostic cutpoints ranging from a fall index of 10 to 20 percent. The ATS convention is to accept a 10 percent maximum fall in $FEV_{1.}$ While outcome reporting included detailed pulmonary function measures, the format was not standardized. Data on the proportion obtaining clinical and complete protection were often missing (Table 2).

Side effect profiles were also poorly reported. While there is evidence for the safety of many of these agents from the chronic asthma literature, it would be prudent for future research to capture adverse effects in the EIB/EIA population. Future trials of interventions to prevent or attenuate EIB/EIA should include clinically relevant secondary outcomes such as patient preferences, symptom scores, and sport performance effects (e.g., changes in athletic performance or endurance). More robust outcome reporting would further inform decision-making by athletes, physicians, and sporting bodies.

Conclusion

Despite exhaustive efforts to identify evidence regarding the diagnostic test characteristics of self-reported history, MCH, sport or venue specific challenges, EVH, FRAST, or mannitol to diagnose patients with EIB/EIA, few studies were found that compared these diagnostic tests to a standardized ECT. The studies that were identified suffered from spectrum bias and considerable variability in test methodology and reported data.

Based on the available data as summarized in this review, none of the six tests provide the diagnostic test characteristics to make them individually attractive as an exclusive alternative to a standardized ECT. There is no clear evidence to suggest that any are equivalent to, or better than, a standardized ECT to diagnose EIB/EIA. More important, given the difference in response by a single individual to multiple challenges, a single negative test should not be used to exclude EIB/EIA. A specificity ranging from 79 to 100 percent in sport specific challenges may indicate they are useful in identifying athletes who do not have EIB/EIA.

Despite exhaustive efforts to locate randomized trials that compared the therapeutic effectiveness of six different interventions for EIB/EIA against placebo, only a small number of studies were identified for each question. The studies that were included suffered from several potential biases; however, this summary represents the most comprehensive review of therapies for EIB/EIA ever reported.

On the basis of this review, we can conclude that the bronchodilator agents examined (SABA, LABA, LTRA, and SAAC) are effective to varying degrees at attenuating or eliminating the drop in FEV_1 associated with EIA. There is evidence of the development of tachyphylaxis associated with 1 to 4 weeks of regular use of SABA and LABA agents but it was not enough to negate their usefulness altogether.

On the basis of this review, we can conclude that the anti-inflammatory agents examined provide mixed results. The evidence suggests that MCS agents are effective in attenuating or eliminating the FEV_1 drop associated with EIA. There is some role for LTRA agents in the treatment of EIA; however, the attenuation appears less than with other bronchodilator agents. There is limited evidence that a single prophylactic dose of ICS is of clinical benefit in preventing EIA. The long-term benefit of ICS agents in asthma is well known, and it is possible that better control of chronic airway inflammation may benefit patients with EIA specifically.[107]

Finally, from the available evidence, it appears that certain warmup protocols are effective at reducing the degree of airway obstruction associated with EIA. Combination warmups show promise; however, it is unclear whether continuous warmups are effective for this condition.

Table 1. Summary of sensitivity and specificity for the diagnostic test accuracy review

Index test	# studies, sample size	ECT type (# studies) Definition of EIB/EIA (# studies)	Sensitivity point estimate or range mean % (95% CI)	Specificity point estimate or range mean % (95% CI)	ECT +ve (≥10% fall FEV_1) N (%)	Index test +ve N (%)	Evidence Grade
Self-report	2, N=206	Treadmill (2)					Very low
		≥10% fall FEV_1 (1)	89% (67, 99)	86% (64, 97)	19 (48)	20 (50)	
		≥15% fall FEV_1 (1)	36% (17, 59)	85% (78, 90)	20 (13)	30 (18)	
Methacholine	16, N=1,048	Treadmill (10) Bicycle ergometer (6)	≥10% fall FEV_1				Moderate
		ECT: ≥8% fall FEV_1 (1), ≥10% fall FEV_1 (6), ≥15% fall FEV_1 (2), ≥18% fall FEV_1 (1), ≥20% fall FEV_1 (5)	0-100%; (MCH_{PC20} <8mg/ml)	0-100%	331 (57)	416 (71)	
		MCH: ≥20% fall FEV_1 at various doses MCH	55-100% (MCH_{PC20} <16mg/ml)	0-100%	420 (53)	498 (63)	
Sport specific challenge	5, N=95	Treadmill (3), bicycle ergometer (2)	≥10% fall FEV_1 Swim challenge		11 (19)	5 (9)	Low
		≥10% fall FEV_1 (4) ≥20% fall FEV_1 (1)	0-50%	83-100%			
			Winter sports n=37 100% (48, 100) (1 study)	79% (49, 95) (1 study)	5 (14)	26 (70)	
Eucapnic voluntary hyperpnea	7, N=138	Treadmill (4), bicycle ergometer (3)	≥10% fall FEV_1				Low
		ECT: ≥10% fall FEV_1 (4), ≥20% fall FEV_1 (1) NR (2)	25-90%	0-71%	42 (30)	74 (54)	
		EVH: ≥10% fall FEV_1 (4), NR (3)					
FRAST	3, N=99	Treadmill (1), bicycle ergometer (2)					Very low
		≥10% fall FEV_1 (1)	≥10% fall FEV_1 : 60-67%	47-67%	13 (38)	18 (53)	
		≥20% fall FEV_1 (2)	≥20% fall FEV_1: 53%	100%	30 (50)	16 (27)	
Mannitol	3, N=423	Treadmill (2), bicycle ergometer (1)	≥10% fall FEV_1	(≥10% fall FEV_1)			Moderate
		ECT: ≥10% fall FEV_1 (3)	58-96%	65-78%	202 (48)	203 (48)	
		Mannitol: ≥15% fall FEV_1 (3)					

ECT = exercise challenge test; EVH = eucapnic voluntary hyperpnea; FEV_1 = forced expiratory volume in 1 second; FRAST = free running asthma screening test; MCH = methacholine; PC = provocative concentration; +ve=positive

Table 2. Prophylactic therapy for EIA: Pulmonary function results

Comparisons Intervention vs. control	N trials (SS_i vs. SS_c) MD % fall FEV_1/PEF (95% CI)*	Clinical protection ≥50% N trials (SS_i vs. SS_c) RR (95% CI)†	Mean % protection of intervention over control (95% CI)	Complete protection N trials (SS_i vs. SS_c) RR (95% CI)†	Evidence Grade
Leukotriene receptor antagonists vs. placebo	N=9 (267 vs.267) 8.9 (6.9, 11.0)	NR	NR	≤10% fall FEV_1 N=4 (124 vs. 123) 1.87 (0.77, 4.56)	Moderate
Inhaled corticosteroids vs. placebo	N=4 (50 vs. 50) 5.0 0.0, 9.9)	NR	BV 6%; BUD 17%; FP 49%	NR	Moderate
MCS (Nedocromil sodium) vs. placebo	N=17 (240 vs. 240) 15.6 (13.2, 18.2)	NR	51 (46, 55)	NR	Moderate
Nedocromil sodium vs. sodium cromoglycate	N=7 (97 vs. 97) 0.9 (-2.7, 4.5)	N=6 (78 vs. 78) 1.12 (0.89, 1.40)	NR	≤10% fall FEV_1 N=6 (78 vs. 78) 1.0 (0.7, 1.4)	Moderate
MCS vs. anticholinergics	N=8 (183 vs. 175) 6.7 (3.3, 10.0)	N=5 (56 vs. 48) 1.35 (1.00, 1.83)	11.2 (2.4, 20.0)	≤15% fall FEV_1 N=8 (177 vs. 169) 1.3 (1.1, 1.6)	Moderate
SABA vs. MCS	N=12 (271 vs. 272) 6.8 (4.5, 9.2)	N=6 (77 vs. 77) 1.4 (1.1, 1.7)	22.7 (11.9, 33.4)	≤15% fall FEV_1 N=9 (225 vs. 226) 1.4 (1.2, 1.8)	Moderate
SABA + MCS vs. SABA	N=5 (40 vs. 40) 1.3 (-6.3, 8.9)	N=3 (37 vs. 37) 0.9 (0.7, 1.1)	10.3 (-27.0, 6.5)	≤15% fall FEV_1 N=4 (44 vs. 44) 0.9 (0.5, 1.4)	Moderate
LABA vs. placebo	N=4 (55 vs. 55) 25.1 (18.0, 32.3)	NR	86%	NR	Moderate
Anticholinergics (Ipratropium bromide) vs. placebo	N=11 (142 vs. 142) 9.8 (5.0, 19.5)	N=6 % achieved=60 (48, 72)	NR	≤10% fall FEV_1 N=7 (74 vs. 74) 4.5 (1.2, 10.9)	Moderate
Interval warmup vs. no warmup	N=4 (56 vs. 56) 10.6 (6.5, 14.7)	NR	NR	≤15% fall FEV_1 N=1 1/12 (8.3%)	Low
Continuous low intensity warmup vs. no warmup	N=3 (37 vs. 37) 12.6 (-1.5, 26.7)	NR	NR	≤15% fall FEV_1 N=1 6/12 (50%)	Low
Continuous high intensity warmup vs. no warmup	N=2 (13 vs. 13) 9.8 (-6.4, 26.0)	NR	NR	NR	Low

BUD = budesonide; BV =Betamethasone valerate; FEV1 = forced expiratory flow in 1 second; FP=fluticasone ICS = Inhaled corticosteroid; LTRA = leukotriene receptor antagonist; MCS = mast cell stabilizers; MD = mean difference; NR = not reported; PEF = peak expiratory flow; RR = risk ratio; SABA = short-acting beta-agonist; SSi = sample size intervention; SSc = sample size comparison.

*a positive MD indicates intervention is better; † RR>1 indicates intervention is better

Evidence Report

Chapter 1. Introduction

What is Exercise-induced Bronchoconstriction and Asthma?

Vigorous physical exercise can be followed by *transient* clinical signs and symptoms of asthma due to airway narrowing. The phenomenon was first recorded around 150 AD by Aretaeus of Cappodocia.[108] Airway obstruction following exercise was first observed among individuals with underlying asthma from which the term *exercise-induced asthma* (EIA) was derived. Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, and it is associated with bronchial (or airway) hyper-responsiveness.[109] Similar post-exercise asthma-like symptoms have been observed in persons without the presence of co-existing asthma, particularly in athletes. In this population the phenomenon has been referred to as *exercise-induced bronchoconstriction* (EIB).[1] In this report we define EIB as "the airway obstruction that occurs in association with exercise without regard to the presence of chronic asthma." We define EIA as "the condition in which exercise induces symptoms of asthma in patients who have asthma."[1] (The two conditions will be discussed separately when the populations are specifically identified; otherwise, for the sake of brevity, they are collectively referred to as EIB/EIA.

The underlying mechanisms of EIB and EIA are multifactorial and complex. Whether the two phenomena have the same pathogenesis is still unknown and continues to be explored.[110,111] In the early 1970s, Chan-Yeung et al.[112] recognized that the severity of the airway constriction was associated with the level of ventilation. In normal nasal breathing, inspired air is heated to body temperature and is completely saturated with water in the first few generations of the airways. There is a marked increase in minute ventilation during and following strenuous exercise and, as a result, the nose is unable to condition the increased volume of air. The added burden on the lower airways, down to the tenth generation and beyond, to warm and humidify the large volume of air triggers osmotic and thermal changes.[20,113,114] Loss of water in the periciliary fluid layer of the airway produces a hyperosmotic environment that may stimulate degranulation of pulmonary mucosa mast cells with subsequent release of several inflammatory mediators such as histamine, leukotrienes, prostaglandin, platelet activating factors, and neuropeptides from sensory nerves.[115] Theorists propose that the released mediators stimulate bronchial smooth muscle spasm[116] and rapid rewarming leads to increased bronchial circulation and engorged capillary beds (or airway edema) that may intensify the obstruction.[114,117,118]

The hallmark of EIB/EIA is that the acute airflow obstruction (measured by the forced expiratory volume in 1 second [FEV_1]) peaks rapidly 3 to 15 minutes after exercise stops and then remits spontaneously within 20 to 60 minutes.[2] It does not cause a prolonged deterioration in lung function. The nature and severity of episodes vary widely within and among individuals and can be influenced by multiple factors (Table 3). Common clinical symptoms include coughing, wheezing, shortness of breath, excessive mucus production, chest tightness, chest pain or an itching or scratching sensation in the chest. Less common symptoms include stomach pain, nausea;[119] and near-death experiences.[120] EIB/EIA has been shown to appear during prolonged exercise causing a lack of endurance despite conditioning. It may influence athletic performance [120,121] and often results in a prolonged recovery time following exercise.[119] A small subset of individuals experience a second, late-phase constriction 4 to 12 hours after the initial activity. This constriction is generally less severe than the first, but the magnitude of the two episodes are

Appendixes cited in this report are provided electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/eibeia/eibeia.pdf

significantly correlated.[108] No single factor predicts who will experience a late response, and these responses do not happen consistently in the same individuals.[108,122]

Approximately 40 to 50 percent of individuals who have an initial episode of EIB/EIA experience a refractory period that is defined as "a period of diminished responsiveness when a second period of exercise follows in 1 to 4 hours."[8] During this time the magnitude of the EIB/EIA response to an identical exercise task may be less than 50 percent of the initial response.[123] This phenomenon is somewhat elusive as it can be present at some times but not at others. The cause is not fully understood but it has been suggested that depletion of catecholamines, increased circulation of prostaglandin, and degranulation of mast cell mediators play a role.

Table 3. Factors that may influence the severity of EIB/EIA

Factor	Decrease EIB/EIA	Increase EIB/EIA
Environmental conditions	Warm temperatures (34-37° C)[124] High humidity (100%) Absence of allergens Low air pollution	Cold temperatures, dry air[124,125] Airborne particles and pollutants, allergens, moulds, dust Irritants: automobile exhaust, sulphur dioxide, nitrogen dioxide, smoke, ozone,[126] chlorine[127]
Type, intensity, duration of exercise	Short episodes of fast/slow running with brief rests[128] VO_2 max <40% predicted[129] <3 minutes continuous exercise	Continuous activities that require near maximum aerobic capacity VO_2 max ≥60% predicted 6-8 minutes continuous exercise
Overall control of underlying asthma and BHR	Good control: FEV_1 >70% predicted Fall in BHR[130]	Poor control: FEV_1 <65% predicted Increase in BHR[130]
Physical conditioning	Good physical conditioning Warmup and cooldown sessions	Poor physical conditioning Sudden burst of activity Fatigue[126] Emotional stress[126] Athletic overtraining[126]
Respiratory tract infections, especially viral	No respiratory tract infections	Presence of respiratory tract infections[126] Sinusitis[130] Rhinitis
Time since last exercise	If within 40-90 min may benefit from refractory period[130]	>2-3 hr
Concurrent medications	Maintenance anti-inflammatory bronchodilator medication	Salicylates, NSAIDS, ß-blockers[130]
Pre-exercise foods eaten	None	Peanuts, celery, shrimp, grain, carrots, bananas[130]

BHR = bronchial hyperresponsiveness

Magnitude and Importance of the Condition

According to National Center for Health Statistics estimates, approximately 20.5 million Americans (seven percent) have asthma.[5] Asthma is reported to have resulted in 4,099 deaths in 2003 and 1.8 million emergency department visits in 2004.[5,131,132] Between 60 to 90 percent of people with asthma experience EIA and consider exercise a major trigger of their asthma symptoms.[133] Some claim that all asthmatics will experience EIA if ventilation is sufficiently high.[6] Prevalence of EIB is lower (six to 13 percent) in a population with no history of asthma or allergy.[8,9]

EIB/EIA gained considerable attention following the 1972 Olympic Games when a gold medalist swimmer, Rick Demont, had his medal rescinded because he took oral ephedrine prior to the race to control his EIB/EIA. Since then, several studies conducted among athletes have reported the prevalence of EIB/EIA to range from 11 to 50 percent.[7] Helenius and Haahtela[9] estimated that the prevalence in summer sport athletes was between 3.7 to 22.8 percent, whereas among winter sport athletes the estimate ranged from 2.8 to 54.8 percent.[134] High level endurance training in sports such as cross-country skiing, swimming, and long distance running may increase bronchial hyper-responsiveness (BHR) and cause inflammation in the airways because these athletes are repeatedly exposed to cold air, inhaled irritants, and allergens.[135]

Asthma is known to have a negative impact on health-related quality of life.[136] The threat of an asthma attack may result in withdrawal from physical and social activities, which can lead to deconditioning, weight gain, and to an altered sense of self-esteem.[137] Both recreational and elite athletes tend to minimize or deny symptoms due to embarrassment, fear of repercussions, or lack of understanding of what they are experiencing.[8,138] EIB/EIA and asthma have an impact on quality of life. The fear of sudden breathlessness creates a sense of panic, which may prevent children and adults from participating in sports and cause parents of children with asthma to impose restrictions.[10] Fear of failure and sub-optimal performance in sports may lead many individuals suffering from EIB/EIA to opt for sedentary activities.[120]

Unrecognized EIB/EIA can result in serious public health consequences. Data compiled from coroners reports for deaths between 1993 to 2000 indicated that, among 61 asthma-related deaths occurring in close relation to physical activity, about 80 percent occurred in individuals younger than 21 years of age. More than half of all asthma-related deaths occurred in individuals who were considered to be elite or competitive athletes, nearly 10 percent of which occurred in individuals with no known history of asthma.[139]

Diagnosis of Exercise-Induced Bronchoconstriction and Asthma

Potential EIB/EIA can be detected by taking a thorough medical history. EIB/EIA is suspected when individuals, who otherwise have good lung function, complain of recurrent shortness of breath and symptoms of cough, wheeze, chest pain, or prolonged recovery time following exercise. These symptoms are independent of a person's conditioning level. If symptoms are relieved by inhaling a short-acting beta-agonist (SABA) or if symptoms are prevented by taking a SABA before exercise, a diagnosis of EIB/EIA is strongly supported.[118] The degree of airway constriction can be measured objectively by a spectrum of pulmonary function tests; however, most clinicians and laboratories use the FEV_1[7] or, very occasionally, the peak expiratory flow (PEF).

When a patient's history suggests EIB/EIA, measuring the change in FEV_1 before and after a standardized exercise challenge test (ECT) on a treadmill or bicycle ergometer can assist in making the diagnosis. The American Thoracic Society (ATS) has published guidelines for conducting a standardized ECT,[18] which include recommendations for environmental control, as well as the level and duration of intensity required to ensure a sufficiently vigorous challenge. Minute ventilation must reach the target level in the first 4 minutes of the challenge.

The standardized laboratory ECT has not always demonstrated sufficient sensitivity to identify EIB/EIA in elite athletes who perform in many venues and with widely varying intensity and duration, therefore, other surrogate tests have been recommended.[140] Some of the current options include sport specific challenges, the free running asthma screening test (FRAST), measures of direct bronchial responsiveness to methacholine (MCH) and indirect responsiveness to eucapnic voluntary hyperpnea (EVH) or mannitol.

In the general population, vigorous exercise should cause little to no prolonged decrease in airflow following exercise. A decrease of 10 percent from baseline has been shown to be a change greater than two standard deviations from the normal response.[141] In 2001, prior to the Salt Lake City Olympics, the International Olympic Committee Medical Commission met to determine the parameters for EIB/EIA. They accepted a cutpoint of a fall of 10 percent or more in FEV_1, as suggested by the European Respiratory Society and ATS guidelines.[18,142] This decision was supported by a study indicating a coefficient of variation of six percent for repeated maneuvers of FEV_1.[143] However, the cutpoint value is a subject of ongoing debate. Two investigators have suggested that a fall in FEV_1 of only 6.5 percent is appropriate.[144,145] Anderson et al. claim that the 10 percent value is justified as this level of constriction could potentially limit exercise performance.[140,145] A 10 percent fall is also supported by Hurwitz et al. who found this degree of constriction to have a specificity of 90 percent for identifying those with asthma.[146]

By convention EIB/EIA is quantified using the maximum percent fall index, which is the maximum reduction in lung function post-exercise, expressed as a percent of the pre-exercise value. The index is calculated using the formula:

$$\frac{FEV_1 / PEF_{pre-exercise} - \text{minimum } FEV_1 / PEF_{post-exercise}}{FEV_1 / PEF_{pre-exercise}} \times 100$$

A fall of 10 percent or greater on an ECT indicates that the individual has EIB/EIA. The greater the reduction in FEV_1, the more severe the EIB/EIA episode is. If a person takes a

prophylactic dose of a medication to control EIB/EIA, "complete protection" is achieved if the percent fall index is less than 10 percent.[147]

A significant placebo effect has been observed in randomized trials comparing an active pre-exercise treatment to placebo. Some participants have obtained either complete protection from EIB/EIA or significant attenuation of it with the placebo alone. Therefore, it is customary to subtract the fall in FEV_1 on the active drug from the fall experienced on placebo and calculate the "clinical protection index" (the degree of protection afforded by a drug expressed as a percent of that offered by placebo) using the following formula:

$$\frac{\text{maximum \% fall } FEV_{1(\text{placebo})} - \text{maximum \% fall } FEV_{1(\text{treatment})}}{\text{maximum \% fall } FEV_{1(\text{placebo})}} \times 100$$

A result of 50 percent or more is regarded as clinically significant.[122]

Treatment of Exercise-Induced Bronchoconstriction and Asthma

The goal of treatment is to prevent or, at least, to reduce the severity of the bronchoconstriction and symptoms so that an individual can participate in any activity, regardless of its intensity and duration, without serious respiratory limitations. Through a combination of education, a commitment to fitness, pharmacologic intervention, and use of nonpharmacologic strategies, EIB/EIA can be successfully managed in the majority of cases. Different pharmaceutical agents that appear to operate on different phases of the response can provide at least partial relief from EIB/EIA.[125] The most commonly used agents are inhaled SABA and long-acting beta-agonist (LABA) agents. Other agents include mast cell stabilizing agents (MCS), short-acting anticholinergics (SAAC), leukotriene receptor antagonists (LTRA), and inhaled corticosteroids (ICS). Theophyllines,[148-150] antihistamines,[151-153] calcium channel blockers,[79,154] heparin,[155] and furosemide[155-158] have also been shown to have some degree of effectiveness.

There are many unresolved issues with respect to the treatment of EIB/EIA with pharmaceutical agents. There is concern that the continuous use of the SABA and LABA agents to control asthma over the long term could lead to a decrease in efficacy when also used prophylactically to control EIA. A development of tolerance, or tachyphylaxis, to SABA or LABA agents may not only decrease their protective effect, but also shorten their duration of action.[62] In the case of SABAs, a serious concern is that continuous use will decrease its impact as a rescue medication in the case of severe EIA.

Objective of this Evidence Report

The objective of this report was to synthesize the evidence to answer six key questions on diagnostic testing for EIB/EIA and six key questions on therapy for EIB/EIA (five involving pharmaceutical interventions and one a nonpharmacologic intervention).

The Key Questions

The key questions for the diagnostic test accuracy review were as follows:

D–1. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of a self-reported history/symptoms diary for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–2. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of a methacholine challenge for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–3. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of sport/venue specific exercise challenges for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–4. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of eucapnic voluntary hyperpnea for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–5. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of a free running asthma screening test (FRAST) for diagnosing EIB/EIA compared with a standardized exercise challenge?
D–6. In patients with suspected EIB/EIA, what are the diagnostic test characteristics of mannitol for diagnosing EIB/EIA compared with a standardized exercise challenge?

The key questions for the therapy review were as follows:

T–1. In patients with confirmed EIB/EIA, do patients using SABA or LABA therapy develop tachyphylaxis to treatment and, if so, at what frequency, compared with standard comparator treatments and/or placebo?
T–2. In patients with confirmed EIB/EIA, does pre-exercise treatment with leukotriene receptor antagonists therapy reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?
T–3. In patients with confirmed EIB/EIA, does pre-exercise treatment with inhaled corticosteroid therapy reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?
T–4. In patients with confirmed EIB/EIA, does pre-exercise treatment with mast cell stabilizers (sodium cromoglycate or nedocromil) therapy reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?
T–5. In patients with confirmed EIB/EIA, does pre-exercise treatment with anticholinergics (ipratropium) therapy reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?
T–6. In patients with confirmed EIB/EIA, does a refractory period (10 to 15 minute warmup and/or cooldown) reduce symptoms and prevent a 10 percent or more drop in FEV_1 compared with no treatment/placebo?

Chapter 2. Methods

In this chapter we document a prospectively developed protocol that was used to conduct this evidence report. A core research team was assembled by the University of Alberta Evidence-based Practice Center (UAEPC). In consultation with the Agency for Healthcare Research and Quality (AHRQ) Task Order Officer (TOO) and the American Academy of Asthma Allergy and Immunology (AAAAI) representative, a Technical Expert Panel (TEP) was assembled to provide content and methodological expertise in the development of this report (Appendix A).

Literature Search and Retrieval

The research librarian, in collaboration with the core research team and TEP, developed search strategies designed to identify evidence relevant to each key question of the report.

For questions relating to the diagnostic test accuracy reviews (Key Questions D–1 to D–6), we systematically searched the following electronic resources: MEDLINE®, EMBASE, EBM Reviews - Cochrane Central Register of Controlled Trials, AMED, PsycINFO, PASCAL, CINAHL®, SPORTDiscus with Full Text, Academic Search Elite, Web of Science®, BIOSIS Previews®, PubMed, Scopus®, the Medion Database of Diagnostic Reviews - University of Maastricht, and Proquest Dissertations and Theses. The original searches were performed between November 5 and 28, 2008. On July 31, 2009, the, the searches were updated using the original search strategies in MEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, PASCAL, SPORTDiscus with Full Text, Web of Science®, BIOSIS Previews®, PubMed, and Scopus®.

Search terms were identified by reviewing search strategies of systematic reviews on similar topics and by looking at how potentially relevant studies were indexed in various databases. A combination of subject headings and text words was adapted for each electronic resource: (exerc* OR train* OR fitness OR physical OR athlete* OR sport*) AND (bronchoconstrict* OR asthma* OR antiasthma* OR wheez* OR “Respiratory Sounds” OR “Bronchial Spasm” OR bronchospas* OR “Bronchial Hyperreactivity” OR “Respiratory Hypersensitivity” OR (bronch* AND spasm*) OR (bronch* AND constrict*) OR (bronchial* OR respiratory OR airway* OR lung*) AND (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficiency)) OR EIB OR EIA. Terms used to limit the searches to diagnostic studies included: diagnos* or predict* or probability or accuracy or sensitivity or specificity. Searches were limited to English language. Date restrictions were not applied. (See Appendix B for exact search strings).

Handsearches were conducted to identify literature from symposia proceedings from the following scientific meetings: AAAAI Annual Meeting (2007–2008), American Thoracic Society (ATS) International Conference (2008), British Thoracic Society (BTS) Winter Meeting (2008), Chest Meeting (2008), and the European Respiratory Society (ERS) Annual Congress (2008). We also searched the last 3 years (2006–2008) of conference proceedings of the American College of Sports Medicine (ACSM) and the Canadian Society for Exercise Physiology (CSEP).

For questions relating to the therapy reviews (Key Questions T–1 to T–6), a comprehensive search was run in the Cochrane Airways Register. The Register contains references to randomized controlled trials (RCTs) from systematic searches of bibliographic databases including Cochrane Central Register of Controlled Trials, Medline®, Embase, Cinahl®, AMED,

PsycINFO, as well as handsearching of respiratory journals and meeting abstracts. The original search was performed on November 5, 2008. On August 4, 2009, the, the search was updated using the original search strategy.

Search terms were identified by reviewing search strategies of systematic reviews on similar topics and by looking at how potentially relevant studies were indexed in various databases. A combination of subject headings and textwords were used: (exerc* OR train* OR fitness OR physical OR athlete* OR sport*) AND (bronchoconstrict* OR asthma* OR antiasthma* OR wheez* OR "Respiratory Sounds" OR "Bronchial Spasm" OR bronchospas* OR "Bronchial Hyperreactivity" OR "Respiratory Hypersensitivity" OR (bronch* AND spasm*) OR (bronch* AND constrict*) OR (bronchial* OR respiratory OR airway* OR lung*) AND (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficiency)) OR EIB OR EIA. We did not apply language or date restrictions. A study design filter was not required as all references in this database are RCTs. (Appendix B). The results from the literature searches were entered into a Reference Manager for Windows bibliographic database version 11.0 (© 2004-2005 Thomson ResearchSoft).

We handsearched abstracts for those years not yet available in the Cochrane Airways Register for the following conference proceedings: AAAAI (2007–2008), ATS International Conference (2008), BTS Winter Meeting (2008), Chest Meeting (2008), ERS Annual Congress (2008). We also searched the last 3 years (2006–2008) of conference proceedings of the ACSM and the CSEP.

To identify ongoing studies we searched ClinicalTrials.gov and ClinicalStudyResults.org. Studies were also identified by checking reference lists of included studies.

Study Selection

Our inclusion/exclusion criteria (Tables 4 and 5) were developed in consultation with the TEP.

Table 4. Inclusion and exclusion criteria for the diagnostic test accuracy review

Study design	Prospective or retrospective studies
Participants	Adults and children aged 6 years and older with suspected EIB/EIA. Recreational and elite athletes are eligible for inclusion.
Index tests	Self-reported history/symptoms diary; methacholine challenge; sport/venue specific exercise challenges; eucapnic voluntary hyperpnea; FRAST; mannitol
Reference standard	Standardized exercise challenge test (treadmill or cycle ergometer) with a drop in FEV_1 of 10% or more from baseline
Outcomes	Studies should provide numeric data for the calculation of diagnostic test characteristics (sensitivity, specificity)

Table 5. Inclusion and exclusion criteria for the therapy review

Study design	Randomized controlled trials (parallel or crossover)
Participants	Adults and children aged 6 years and older with confirmed EIB/EIA. Recreational and elite athletes are eligible for inclusion.
Interventions	*Pre-exercise pharmacologic therapy:* For Key Question T-1: regular use (≥1 wk) SABA or LABA. For Key Questions T-2 to T-5: single-dose prophylactic use of leukotriene receptor antagonists, inhaled corticosteroids, mast cell stabilizers, short-acting anticholinergics *Nonpharmacologic therapy:* refractory period (pre-exercise warmup and/or cooldown)
Comparator	For Key Question T-1, any standard comparator treatments and/or placebo. For Key Questions T-2 to T-6, no treatment or placebo.
Outcomes	Maximum percent fall in FEV_1 or PEF from pre-exercise baseline, symptoms, presence or absence of EIB/EIA (complete protection), clinical protection, adverse effects

We used a two-step process for article screening. First, two reviewers independently screened the titles and abstracts (when available) to determine if an article met broad inclusion criteria. Each article was rated as "include," "exclude," or "unclear." The full-text of all articles classified as "include" or "unclear" were retrieved for formal review. Second, two reviewers independently assessed each study using a standard inclusion/exclusion form (Appendix C). Disagreements were resolved through discussion between the two reviewers or third party adjudication, as needed.

Assessment of Methodological Quality

We assessed the methodological quality of the diagnostic test accuracy studies using the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) tool.[11] This tool comprises 14 items that assess several common sources of bias in diagnostic studies, including spectrum bias, selection bias, information bias, verification bias, misclassification bias, disease progression bias, and excluded data. For the purpose of this review, we chose to include only 13 of the QUADAS items. A priori, we determined that the question regarding incorporation bias did not apply because none of the index tests under review were incorporated in the reference standard. Each item in the QUADAS tool is scored as "yes," "no," or "unclear." In addition, the source of funding (e.g., industry, government, other) for each study was recorded.[159] Results of the quality assessment are presented in the text and a table for each of the individual key questions (D–1 to D–6).

We assessed the methodological quality of RCTs included in the therapy review using the Jadad[12] scale and Schulz's criteria to assess allocation concealment.[13,14] Components of the 5-point Jadad scale include randomization, double blinding, and reporting of withdrawals and dropouts. Allocation concealment was assessed and scored as "adequate," "inadequate," or "unclear." In addition, the source of funding for each study (e.g., industry, government, other) was recorded.[159] Results are presented in the text and a table for each of the individual key questions (T–1 to T–6).

The methodological quality of included studies was assessed independently by two reviewers. Decision rules regarding application of the quality assessment tools were developed a priori (Appendix C). Discrepancies were resolved through discussion between the two reviewers or third party adjudication, as needed.

Grading the Body of Evidence

For the diagnostic test accuracy reviews, we graded the available evidence for each key question using the GRADE system for rating the quality of evidence and strength of recommendations for diagnostic tests.[15] We assessed the strength of the study designs, the quantity and quality of individual studies, and the consistency and precision of the results. We also assessed the indirectness of evidence. For all studies, the outcomes were measures of test accuracy (i.e., true positive, true negative, false positive, false negative), which are surrogates for patient-important outcomes. We determined that true positive and true negative results would improve outcomes that are important to patients. True positive results will lead to administration of effective, safe prophylactic treatment for EIB/EIA; true negative results will spare patients unnecessary treatment or further testing for EIB/EIA. We identified uncertainty about the consequences of false positive results which could lead to unnecessary treatment for EIB/EIA and the potential exclusion of individuals from participating in sports or working in occupations requiring heavy physical demands. We also determined that there was uncertainty about directness for false negative results related to delayed access to prophylactic and/or rescue treatments, ongoing symptoms of EIB/EIA, underperformance in physical activity, and reduced quality of life leading to avoidance of physical activities and sports. This uncertainty about directness resulted in a reduction in the quality of evidence. For each key question the quality of evidence was graded as high, moderate, low or very low.

For the therapy reviews, the strength of evidence for the primary outcome (maximum percent fall in FEV_1 from baseline) was assessed for each key question using the EPC approach to grading the strength of a body of evidence.[16] This approach assesses the evidence based on four domains: risk of bias, consistency, directness, and precision. We classified the strength of evidence as high, moderate, low, or insufficient.

Data Extraction

Data were extracted using standard forms (Appendix C) by one reviewer and checked for accuracy and completeness by a second reviewer. Data extracted for each study included details of study design and inclusion/exclusion criteria, details of the population, details of the index test and reference standard (for the diagnostic test accuracy reviews), intervention and comparator (for the therapy reviews), and results obtained for various outcomes. Reviewers resolved discrepancies in data extraction by consensus or in consultation with a third party.

Data Analysis

The following data assumptions were made and imputations performed to transform reported data into the form required for this report. Graph extraction was performed using CorelDRAW® 9.0 (Corel Corp., Ottawa, Canada). Means were approximated by medians, and 95 percent empirical intervals were used to calculate approximate standard deviations (SD). Because the majority of the included studies in the therapy reviews used a crossover design, standard errors of mean differences were either computed exactly using individual patient data (IPD) or imputed using an estimated within-patient correlation of 0.5.

Diagnostic Test Accuracy Review

Our reference standard was a standardized ECT- either using a treadmill or bicycle ergometer. Our threshold for a positive test on the ECT was a fall in FEV_1 of 10 percent or more from a pre-exercise baseline.[18] Thresholds of 15 percent and 20 percent were examined in sensitivity analyses. The threshold for a positive test for the methacholine challenge was a 20 percent or more drop in FEV_1 at a provocative concentration of less than 8 mg/ml (PC_{20}).[18] For mannitol the threshold was a 15 percent drop in FEV_1 at less than 635mg or a drop of 10 percent between consecutive doses.[23] The threshold for a positive test for EVH, FRAST and sport/venue specific challenges was a fall in FEV_1 of 10 percent or more. Where data were available we conducted sensitivity analyses using a different threshold dose for methacholine (less than 16 mg/ml). True positives, false positives, true negatives, and false negatives were recorded for each of the six index tests. These data were used to calculate sensitivity and specificity for each study. We present individual study results graphically by plotting the estimates of sensitivity and specificity and their 95 percent confidence intervals (95 percent CI) in forest plots. Where there were more than five studies, we plotted the sensitivity and specificity in receiver operating characteristic (ROC) space and present a summary ROC curve. Area under the curve (AUC) was estimated.

Because many of the studies presented IPD, we were able to use our thresholds for both reference and index tests for our primary and sensitivity analyses. Where no IPD were available and a different threshold was used by the study authors, we presented a qualitative summary of the results of the study.

Planned subgroup analyses included age (children [less than 18 years old] versus adult [18 years and older]), different thresholds for positive results, and patients with EIB versus EIA.

Therapy Review

For studies assessing therapy of the five treatments compared with a control or placebo, a mean difference (MD) was calculated for continuous variables and a risk ratio (RR) was calculated for dichotomous variables. Results are reported with accompanying 95 percent CI.

Meta-analyses were conducted using the random effects model where appropriate. The I^2 statistic was used to assess heterogeneity.[17] Planned subgroup analyses included age (children [less than 18 years old] versus adult [18 years and older]), severity of EIB/EIA as defined by the percent fall index on placebo (mild [less than 30 percent] versus moderate-severe [30 percent or more]), and patients with EIB versus EIA.

Sensitivity analyses were conducted to assess the robustness of the findings across study quality.[160] When meta-analyses had sufficient studies, publication bias was tested visually using the funnel plot. All data pooling was performed using Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).

Peer Review

Eight experts in the field (Appendix A) agreed to peer review the draft report and provide comments. Reviewer comments were considered by the UAEPC in preparation of the final report. All peer reviewer comments and the UAEPC disposition of comments were submitted to AHRQ for assessment and approval.

Chapter 3. Results

Diagnostic Test Accuracy Review

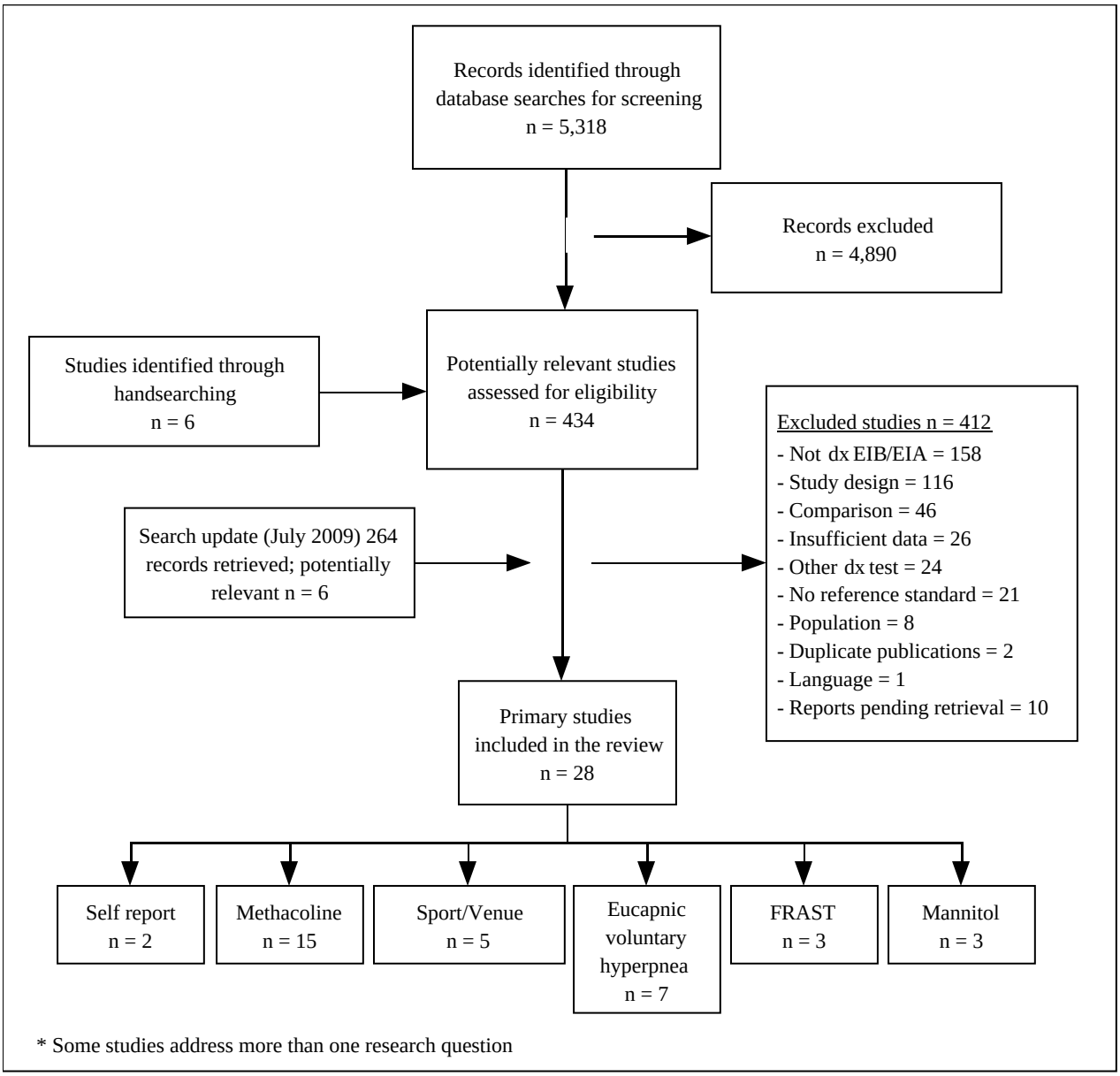
Literature Search

The search strategy for the diagnosis of EIB/EIA identified 5,318 citations from electronic databases and six additional references by handsearching (Figure 1). Screening these titles and abstracts identified 434 potentially relevant references. Ten studies could not be retrieved (Appendix D). Most of these were abstracts that were only available in supplementary issues of journals; they were requested through interlibrary loan but did not arrive by the time this report was written. The search update identified an additional six studies for further evaluation. Overall 28 studies met the inclusion criteria for this report; 412 studies were excluded. The included studies addressed the following research questions: self-report (n=2),[21,22] methacholine (MCH) challenge (n=15),[23-37] sport/venue specific challenges (n=54),[34,38-41] eucapnic voluntary hyperpnea (EVH; n=7),[34,38,39,42-45] FRAST (n=3),[36,40,46] and mannitol (n=3).[23,47]

The main reasons for excluding studies were (1) the diagnostic technique did not assess EIB/EIA (n=158), (2) inappropriate study design (n=116), (3) there was no comparison group (n=46), (4) there were insufficient data to construct a 2x2 table (n=26), (5) the study assessed other diagnostic tests that were not included in this report (n=24), and (6) there was an inappropriate reference standard (n=21). Eleven studies were excluded for other reasons. The list of excluded studies and reasons for exclusion are identified in Appendix D.

Appendixes cited in this report are provided electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/eibeia/eibeia.pdf

Figure 1. Diagnosis of EIB/EIA: Flow diagram for study retrieval and selection



Key Question D–1: Self-Reported History or Symptoms Diary

Description of Included Studies

Two studies[21,22] met the inclusion criteria for the diagnostic test accuracy review of self-reported history/symptoms diary compared with a standardized exercise challenge test (ECT). Tables 6 and 7 summarize the study and participant characteristics.

In the study by Frobase et al.[21] 20 junior high school athletes (11 to 15 years) who responded "yes" to the question "do you experience cough after exercise?" were included. They were matched to 20 controls who responded "no" to the same question. All participants underwent a treadmill ECT. They ran for 6 minutes at an intensity of 85 to 90 percent of predicted maximum heart rate. No information about a history of asthma was provided.

In the study by Rupp et al.[22] 166 high school athletes (12 to 18 years) completed a self-report questionnaire that included two questions relevant to EIB/EIA ("do you have trouble breathing after running 1 mile and resting?" and "do you have to stop when running for ½ mile?"). Forty-eight students (29 percent) were identified as being at risk for EIB/EIA based on baseline spirometry or by clinical history. All participants underwent a treadmill ECT. They ran for 6 minutes after reaching 80 percent of their predicted maximum heart rate.

Methodological Quality of the Included Studies

Table 8 summarizes the methodological quality of the included studies. The number of "unclear" responses for both studies raises questions regarding bias and generalizability. Neither study had a representative patient spectrum which suggests the possibility of spectrum bias. Blinding to the results of the ECT and the index test was not reported. There were no details about uninterpretable or indeterminate index test results. One study[22] did not report their source of funding; one[21] was supported by government grants. The body of evidence is classified as "low."

Quantitative Results

The two studies used different thresholds to define a positive result on the ECT. Using a threshold of a maximum percent fall in FEV_1 of 10 percent or more, Frobase et al.[21] reported a sensitivity of 89 percent (95 percent CI: 67, 99) and a specificity of 86 percent (95 percent CI: 64, 97). In the study group, 17 (85 percent) participants had a positive ECT; in the control group 2 (10 percent) had a positive ECT.

Using a threshold of 15 percent or more, Rupp et al.[22] reported a sensitivity of 36 (95 percent CI: 17, 59) and specificity of 85 percent (95 percent CI: 78, 90). Twenty participants (13 percent) had a positive ECT; 30 (18 percent) were at risk of EIB/EIA based on the questionnaire.

Table 6. Description of studies in the diagnostic test accuracy review: Self-report vs. ECT

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (min) Load; Environmental conditions Follow-up time points Author definition of EIB	INDEX TEST (Self-report) Type; Description
Frobase[21] 1992	Case control (prospective); self-report first NR; NR NR NR	Treadmill; 6 85-90% max HR; NR PEF at 3 min intervals up to 15 min ≥10% fall FEV_1	Do you experience cough after exercise?
Rupp[22] 1993	Cross sectional (prospective); self-report first NR; NR; all ECT completed in 1 mo period Aug-Sept 1990; back to back NR	Treadmill; 6 6 mph, 10% grade after HR reached 170 bpm; 45-55% RH, air conditioned 22-25°C After 1 min cooldown, 1, 10, 20, 30 min ≥15% fall FEV_1	Determination of risk for EIB/EIA based on 3 components of pre-challenge evaluation: self-report questionnaire, physician interview, and resting PFT; participants categorized as 'at risk' if FEV_1 or FVC ≤80% of predicted values or if FEV_1 to FVC ratio ≤0.80

bpm = beats per minute; C = Celsius; ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = heart rate; max = maximum; min = minute(s); mph = miles per hour; NR = not reported; PFT = pulmonary function test; RH = relative humidity

Table 7. Description of participants in the diagnostic test accuracy review: Self-report vs. ECT

Author Year	Participants enrolled (N); analyzed (N) Age (range) Males: N (%)	Recruitment Country Index of activity (fitness level)	History of asthma N (%); Asthma severity; Atopic status N (%); History of ICS History of EIB/EIA	Baseline lung function (FEV_1) Baseline FEV_1 (% predicted)
Frobase[21] 1992	20; 20 11-15 NR	Junior high school students answering yes to "Do you cough after exercise?" U.S. NR	NR; NR NR NR NR	NR NR
Rupp[22] 1993	166; 166 12-18 121 (72.8)	High school (students in athletic program) U.S. High school athletes	NR; NR NR NR NR	NR NR

EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; NR = not reported

Table 8. Methodological quality of the studies in the diagnostic test accuracy review: Self-report vs. ECT

Author Year	Representative spectrum	Selection criteria defined	Acceptable reference standard	Timing bias avoided	Partial verification avoided	Differential verification avoided	Clear reporting of index test	Clear reporting of reference standard	Index test blinded	Reference standard blinded	Clinical data	Uninterpretable results reported	Withdrawals explained
Frobase[21] 1992	No	No	Yes	Yes	Yes	Yes	Yes	U	U	U	U	U	Yes
Rupp[22] 1993	U	U	Yes	Yes	Yes	Yes	U	Yes	U	U	U	U	Yes

U = unclear

Key Question D–2: Methacholine Challenge

Description of Included Studies

Fifteen studies[23-37] met the inclusion criteria for the diagnostic test accuracy review of a methacholine (MCH) challenge compared with a standardized exercise challenge test (ECT). All studies were conducted prospectively. Twelve used a cross sectional study design,[23-25,27-32,34-36] three[26,33,37] used a case-control design. One was published as a meeting abstract;[24] fourteen were published in peer reviewed journals. The median year of publication was 1994 and ranged from 1973 to 2009. Studies were conducted in Europe,[27,29-31,34,35,37] the United States,[23,26,28] the Middle East,[24,25] Asia,[32,33] and South America.[36]

The characteristics of the studies are summarized in Table 9. The standardized ECT was performed on a treadmill[23-28,30,32-34] or a bicycle ergometer.[29,31,35-37] A positive test was defined at five different cutpoints using the maximum percent fall in FEV_1 of 8 percent or greater,[25] 10 percent or greater,[23,24,30,34,36,37] 15 percent or greater,[27,31] 18 percent or greater,[28] and 20 percent or greater.[26,29,32,33,35] Most studies reported the target workload as between 80 to 90 percent of maximum predicted heart rate. In one study the target workload was described as "to exhaustion"[34] and in another "target ventilation output of more than 60 percent of predicted maximum voluntary ventilation."[37] For two studies, the target workload was not reported.[24,25]

MCH challenges were based on the 2 minute tidal breathing method[25,27,29,30,35] or the five breath dosimeter method.[23,26,28,32-34,36,37] For the remaining studies, the protocol was either specific to the particular study group or was not clearly described.[24,31]

The baseline characteristics of the participants are presented in Table 10. The number of participants in each study ranged from 12 to 375 (median=52; IQR 28, 59). Six studies involved adults,[26,28,31,33,34,37] seven involved children,[24,27,29,30,32,35,36] and two included both adults and children.[23,25] One study focused on elite female swimmers[34] and one on endurance athletes.[37] The remaining studies did not report on the level of fitness or sports participation. Most studies included participants who had a history of asthma.[23-26,28,29,31-33,35,36] Generally, asthma was mild to moderate and stable. For the studies that used a case-control design,[26,33,37] the control group comprised healthy controls who had no history of asthma.

Methodological Quality of Included Studies

Table 11 summarizes the methodological quality of the included studies. There are several methodological issues in this group of studies. Of concern is the risk of spectrum bias. Most studies did not report how participants were recruited into the study, nor did they describe the inclusion criteria; three studies recruited volunteers.[26,30,34] Blinding of results of the ECT to the results of the MCH challenge was not reported. Seven studies did not report their sources of funding.[24,25,27-29,35,36] Four studies received funding support from industry,[23,30-32] and six were supported by government and/or institution grants.[26,30,31,33,34,37] The body of evidence is classified as "moderate."

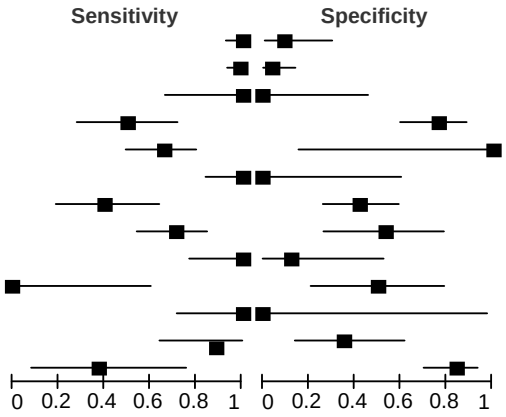
Quantitative Results

We analyzed the data using two concentration thresholds for MCH: PC_{20} MCH less than 8 mg/ml and PC_{20} MCH less than 16 mg/ml. Regardless of the threshold, there was considerable heterogeneity across the studies. Using the PC_{20} MCH less than 8 mg/ml threshold 331 (57

percent) tested positive for EIB/EIA on the ECT; 416 (71 percent) were positive on the MCH challenge. Sensitivity and specificity both ranged from 0 to 100 percent. (Figure 2)

Figure 2. Forest plot of sensitivity and specificity: Methacholine challenge vs. ECT (PC_{20} MCH less than 8 mg/ml; FEV_1 fall index 10 percent or more for ECT)

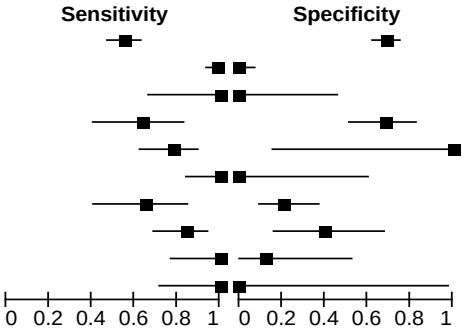
Study	TP	FP	FN	TN	Sensitivity	Specificity
Avital 1989	49	19	0	2	1.00 [0.93, 1.00]	0.10 [0.01, 0.30]
Avital 2000	80	45	1	2	0.99 [0.93, 1.00]	0.04 [0.01, 0.15]
Chatham 1982	9	6	0	0	1.00 [0.66, 1.00]	0.00 [0.00, 0.46]
Clough 1990	11	9	11	29	0.50 [0.28, 0.72]	0.76 [0.60, 0.89]
Eggleston 1979	27	0	14	2	0.66 [0.49, 0.80]	1.00 [0.16, 1.00]
Foresi 1986	21	4	0	0	1.00 [0.84, 1.00]	0.00 [0.00, 0.60]
Henriksen 2002	8	22	12	16	0.40 [0.19, 0.64]	0.42 [0.26, 0.59]
Koh 1996	27	7	11	8	0.71 [0.54, 0.85]	0.53 [0.27, 0.79]
Lin 1991	14	7	0	1	1.00 [0.77, 1.00]	0.13 [0.00, 0.53]
Pedersen 2008	0	6	4	6	0.00 [0.00, 0.60]	0.50 [0.21, 0.79]
Sekerel 1997	11	1	0	0	1.00 [0.72, 1.00]	0.00 [0.00, 0.97]
Souza 2005	12	11	1	6	0.92 [0.64, 1.00]	0.35 [0.14, 0.62]
Verges 2005	3	7	5	37	0.38 [0.09, 0.76]	0.84 [0.70, 0.93]



Using the PC_{20} MCH less than 16 mg/ml threshold 420 (53 percent) tested positive for EIB/EIA on the ECT; 498 (63 percent) were positive on the MCH challenge. Heterogeneity in sensitivity estimates was reduced somewhat (range 55 to 100); specificity still ranged from 0 to 100 percent (Figure 3).

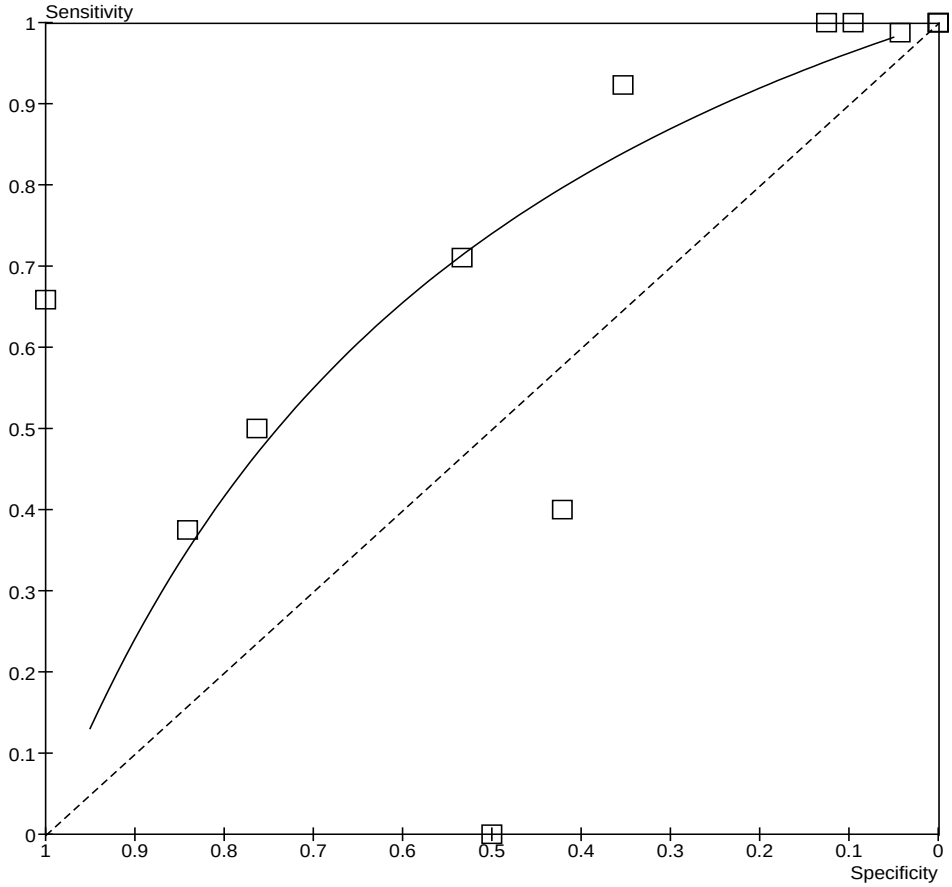
Figure 3. Forest plot of sensitivity and specificity: Methacholine challenge vs. ECT (PC_{20} MCH less than 16 mg/ml; FEV_1 fall index 10 percent or more for ECT)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Anderson 2009	90	66	73	146	0.55 [0.47, 0.63]	0.69 [0.62, 0.75]
Avital 2000	80	47	1	0	0.99 [0.93, 1.00]	0.00 [0.00, 0.08]
Chatham 1982	9	6	0	0	1.00 [0.66, 1.00]	0.00 [0.00, 0.46]
Clough 1990	14	12	8	26	0.64 [0.41, 0.83]	0.68 [0.51, 0.82]
Eggleston 1979	32	0	9	2	0.78 [0.62, 0.89]	1.00 [0.16, 1.00]
Foresi 1986	21	4	0	0	1.00 [0.84, 1.00]	0.00 [0.00, 0.60]
Henriksen 2002	13	30	7	8	0.65 [0.41, 0.85]	0.21 [0.10, 0.37]
Koh 1996	32	9	6	6	0.84 [0.69, 0.94]	0.40 [0.16, 0.68]
Lin 1991	14	7	0	1	1.00 [0.77, 1.00]	0.13 [0.00, 0.53]
Sekerel 1997	11	1	0	0	1.00 [0.72, 1.00]	0.00 [0.00, 0.97]



The area under the curve (AUC) of the ROC curve was marginally more than 0.5 using a 10 percent fall in FEV_1 for a positive ECT and a PC_{20} MCH of less than 8 mg/ml (Figure 4) for a positive MCH. There was no improvement in the AUCs for any of the FEV_1 cutpoints (10, 15 or 20 percent) or the MCH threshold (data not shown).

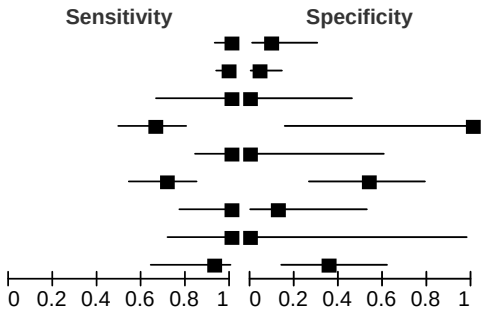
Figure 4. ROC curve plotting sensitivity vs. specificity: Methacholine challenge vs. ECT (PC_{20} MCH less than 8 mg/ml; FEV_1 fall index 10 percent or more for ECT)



To explore heterogeneity, we performed a subgroup analysis on studies in which all participants had a diagnosis of asthma.[24-26,28,29,32,33,35,36] This analysis (Figure 5) reduced the heterogeneity in sensitivity somewhat (range from 66 to 100); however, specificities ranged from 0 to 100 percent. Among this group of participants, 277 (70 percent) tested positive for EIA on the ECT; 350 (88 percent) were positive to the MCH challenge.

Figure 5. Forest plot of sensitivity and specificity: Methacholine challenge vs. ECT in studies in which all patients had asthma (PC_{20} MCH less than 8 mg/ml; FEV_1 fall index 10 percent or more for ECT)

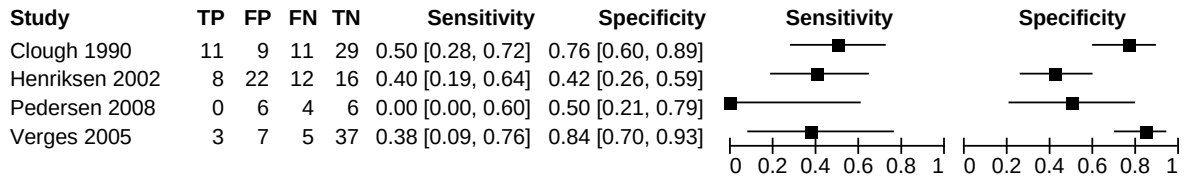
Study	TP	FP	FN	TN	Sensitivity	Specificity
Avital 1989	49	19	0	2	1.00 [0.93, 1.00]	0.10 [0.01, 0.30]
Avital 2000	80	45	1	2	0.99 [0.93, 1.00]	0.04 [0.01, 0.15]
Chatham 1982	9	6	0	0	1.00 [0.66, 1.00]	0.00 [0.00, 0.46]
Eggleston 1979	27	0	14	2	0.66 [0.49, 0.80]	1.00 [0.16, 1.00]
Foresi 1986	21	4	0	0	1.00 [0.84, 1.00]	0.00 [0.00, 0.60]
Koh 1996	27	7	11	8	0.71 [0.54, 0.85]	0.53 [0.27, 0.79]
Lin 1991	14	7	0	1	1.00 [0.77, 1.00]	0.13 [0.00, 0.53]
Sekerel 1997	11	1	0	0	1.00 [0.72, 1.00]	0.00 [0.00, 0.97]
Souza 2005	12	11	1	6	0.92 [0.64, 1.00]	0.35 [0.14, 0.62]



In the subgroup of four studies in which fewer than 50 percent of participants had asthma[27,30,34,37] heterogeneity remained (Figure 6). Sensitivity ranged from 0 to 50 percent and

specificity from 42 to 84 percent. Among this group of participants, 54 (29 percent) tested positive for EIB/EIA on the ECT; 66 (35 percent) were positive to the MCH challenge. Of note, the study by Pedersen et al.[34] focused on elite swimmers; when this study was excluded, sensitivity ranged from 38 to 50 percent and specificity from 42 to 76 percent.

Figure 6. Forest plot of sensitivity and specificity: Methacholine challenge vs. ECT in studies in which less than 50 percent of patients had asthma (PC_{20} MCH less than 8mg/ml; FEV_1 fall index 10 percent or more for ECT)



We also explored the following possible sources of heterogeneity: adults versus children, treadmill versus bicycle ergometer ECT, the five breath dosimeter versus 2 minute tidal breathing method for the MCH challenge, and cold/dry air versus other conditions during the ECT. There was no improvement in heterogeneity for any of these subgroups.

Table 9. Description of studies in the diagnostic test accuracy review: Methacholine vs. ECT

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (min) Load; Environmental conditions Follow-up time points Author definition of EIB	INDEX TEST (MCH challenge) Type; Description Follow-up time points Author definition of EIB
Anderson[23] 2009	Cross sectional (prospective); ECT first 5 visits; 1; ECT - MCH: 1-2 d; ECT - Mannitol: 1-2 d; MCH - Mannitol: 1 d NR	Treadmill; 6 80-90% max H; medical grade dry air from Douglas bag; 20-25°C Pre-ECT, 5, 10, 15, 30 min post ECT ≥10% fall FEV_1	5 breath dosimeter method; increasing concentrations from 0.0312–16 mg/ml; measured within 3 min after each concentration NR PC_{20} MCH ≤16 mg/ml
Avital[24] 1989	Cross sectional (prospective); NR 2; 1; 2 within a 2 mo period NR	Treadmill; 6 6 km/hr at 10% slope RH and temp NR NR ≥10% fall FEV_1	Steady state tidal breathing technique; concentrations and time NR NR PC_{20} MCH <8 mg/ml
Avital[25] 2000	Cross sectional (prospective); MCH first Varied; 3; 85% within 7 d; 15% within 30 d Withheld: Bronchodilators ≥12 hr; SCG ≥20 hr; ICS continued unchanged	Treadmill; 6 (5 km/h, 10% slope) NR RH 48-56%; 22-26°C Pre-ECT, 1, 3, 5, 10, 15 min post ECT ≥8% fall FEV_1	2 min tidal breathing method; increasing concentrations from 0.03–32 mg/ml measurements at 30, 90, 180 sec after each inhalation NR PC_{20} MCH <8 mg/ml
Chatham[26] 1982	Case-control (prospective); MCH first 2; all within 48 hr; 24 hr Withheld: bronchodilators, methylxanthines, antihistamines x 72 hr	Treadmill; 6 90 max HR RH 40.1±13.3%; 22.3±1°C Pre-ECT, 5, 15, 30, 60 min post ECT ≥20% fall FEV_1	5 breath dosimeter method; increasing concentrations from 0.156–25 mg/ml in 7 increments NR PC_{20} MCH
Clough[27] 1991	Cross sectional (prospective); Randomized order: half MCH first, half ECT first 2; 1; 24 hr Withheld: $beta_2$-agonists x 6 hr; all other med. x 24 hr	Treadmill; 6 4.8 km/hr, 15% slope; 90% max HR RH NR; air conditioned room Pre-ECT, 3, 5, 10 min post ECT ≥15% fall FEV_1	2 min tidal breathing method; doubling concentrations from 0.025–6.4 µmol NR PC_{20} MCH <6.4 µmol

bpm = beats per minute; C = Celsius; d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; hr = hour(s); HR = heart rate; km/hr = kilometers per hour; ICS = inhaled corticosteroids; m = meters; µmol = micromole; max = maximum; mcg = microgram; MCH = methacholine; med = medication(s); mg/ml = milligram per milliliter; min = minute(s); mo = month(s); mph = miles per hour; NR = not reported; PC_{20} = provocative concentration causing a 20% fall in FEV_1; PEF = peak expiratory flow; PSI = pounds per square inch; RH = relative humidity; rpm = revolutions per minute; SABA = short-acting beta-agonist; SCG = sodium cromoglycate; SD = standard deviation; sec = seconds; temp = temperature; wk = week(s)

Table 9. Description of studies in the diagnostic test accuracy review: Methacholine vs. ECT (continued)

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (minutes) Load; Environmental conditions Follow-up time points Author definition of EIB	INDEX TEST Type; Description Follow-up time points Author definition of EIB
Eggleston[28] 1979	Cross sectional (prospective); ECT first NR; NR; <3 mo Withheld: SABA x 8 hr; LABA x 12 hr; SCG x 2 wk	Treadmill; 5 90% max HR RH and temp NR Pre-ECT, 1, 5, 10, 15, 20 min post ECT ≥18% fall FEV_1	5 breath dosimeter method; concentrations NR; 1.5 and 3 min after each NR PC_{20} MCH
Foresi[29] 1986	Cross sectional (prospective); MCH first 3; 1; 48 hr 19 on no drugs or SABA as necessary; 2 on SABA (200 mcg 4 /d); 3 on IB 80 mcg + SABA 200 mcg 4 /d Withheld: all x 12 hr	Bicycle ergometer; 6 Resistance of 2.0 - 3.5 watts/kg; workload=90% max HR RH ≤50%; 22°C Pre-ECT, immediately after, 5 min intervals x 30 min post ECT >20% fall FEV_1	2 min tidal breathing method; doubling concentrations from 0.03 – 65 mg/ml; before, 0.5, 1.5, 3 min after each inhalation PC_{20} MCH
Henriksen[30] 2002	Cross sectional (prospective); ECT first 2; 1; 2-7 d after d 1 NR	Treadmill; 6 to 8 5.5% incline; load increased during 1st 2 min by increasing speed to HR of 180 bpm; load further increased to 90% max HR of 220 bpm minus age during last 4 min RH mean 34%, range 33-35%; mean 22°C, range 20-24°C Pre-ECT immediately after, 3, 6, 10, 15 min post ECT ≥10% fall FEV_1	2 min tidal breathing method; cumulative dose of 2 mg MCH in 5 increments NR PC_{20}.MCH
Kiviloog[31] 1973	Coss sectional (prospective); MCH first 1; 2 (MCH in am; ECT in pm); at least 4 hr Withheld: steroids x 8 hr; bronchodilators, coffee, tea, antihistamines, anticholinergics x 24 hr	Bicycle ergometer; load increased every 6 min by 49 (males) or 33 watts (females) to exhaustion (80-102%); RH mean 41, range 15-66%; mean 19°C, range 18-25.5°C, no fan used 2, 6, 10, 15, 30 min post-exercise ≥15% fall in PEF for ECT within 10 min of termination	Concentrations of 0.025 (x5 inhalations), 0.25 (x5), 0.25 (x15), 2.5 (x5); inhale deeply for 2 sec at each breath NR Decrease in PEF by ≥15% below baseline within 3 min of termination of inhalation; MCH negative response decrease at 2.5% concentration

Table 9. Description of studies in the diagnostic test accuracy review: Methacholine vs. ECT (continued)

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (min) Load; Environmental conditions Follow-up time points Author definition of EIB	INDEX TEST Type; Description Follow-up time points Author definition of EIB
Koh[32] 1996	Coss sectional (prospective); ECT first 2 consecutive d; 1; 17 hr (d1=MCH test at 4 pm; d2=ECT at 9 am) Withheld: no meds or caffine on test day; ICS x 24 hr; cromolyn sodium x 7d	Treadmill; 6 80-90% max HR (slope/speed adjusted) RH NR; no variations in environmental temp, air conditioned, 3-10 min apart until 60 min post-ECT ≥20% fall FEV_1	5 breath dosimeter method; increasing concentrations from 0.075–150 mg/ml in 12 increments; measured 60-90 sec after inhalation NR PC_{20} MCH
Lin[33] 1991	Case-control (prospective); ECT first 2; 1, then 4; MCH then ECT 1-3 wk later NR	Treadmill; 6 3 mph at 10% incline, adjusted until HR reached 90% predicted age max for 4 min RH and temp NR Pre-ECT, 5, 10, 15, 20, 25, 30 min post ECT ≥20% fall FEV_1	5 breath dosimeter method; increasing concentrations from 0.1–25.0 in 7 increments NR PC_{20}.MCH
Pedersen[34] 2008	Cross sectional (prospective); NR 4 visits; NR; at least 24 hr apart NA	Treadmill; 5±1.1 Ran until exhausted at constant speed with gradiant increasing 2% every 2 min RH and temp NR Pre-ECT, 1, 3, 5, 10, 15, 20 min post ECT ≥10% fall FEV_1	5 breath dosimeter method; concentrations NR; measured after each inhalation NR PC_{20}.MCH ≤2µmol (~4 mg/ml)
Sekerel[35] 1997	Cross sectional (prospective); randomized order of tests 3; 1; within 1 wk at same time of d Withheld: oral med x 24 hr; inhaled med x 12 hr	Bicycle ergometer; 6 90% max HR RH and temp NR 1, 5, 10, 15, 20 min post ECT ≥20% fall FEV_1	2 min tidal breathing method; increasing concentrations starting at 0.03 mg/ml; measured at 0.5 and 1.5 min after each inhalation NR PC_{20}.MCH
Souza[36] 2005	Cross sectional (prospective); randomized order of tests 3; 1 (all 8-10 am); min 24 h to 10 d Withheld: coffee, tea, drinks with caffine x 2 hr; SABA x 12 h; antihistamines x 48 hr (short-acting) x 5 d (long-acting)	Bicycle ergometer; 6 (nose clips) 80-90% max HR after 1-2 min warmup (target 178±7 bpm) compressed air RH ~50%; 21.1±1°C 3, 6, 10, 15, 20, 30 min post ECT ≥10% fall FEV_1	5 breath dosimeter method; increasing concentrations from 0.25–25 mg/ml in 6 increments NR PC_{20} MCH ≤6.6µ mol
Verges[37] 2005	Case-control (prospective); MCH first 1; 6; mean interval of 6.2±1.5 hr (range=4-10 hr) between MCH and ECT Withheld: SABA x 48 hr; ICS x 3 wk	Bicycle ergometer; 12 at >60% max HR, voluntary ventilation (35 x FEV_1) RH dry medical air; NR Pre-ECT, 1, 3, 5, 7, 10, 15 min post ECT ≥10% fall FEV_1	5 breath dosimeter method; increasing concentrations from 0.0156–4 mg in 6 increments; measured 2 min after each inhalation NR PC_{20} MCH <4 mg

Table 10. Description of participants in the diagnostic test accuracy review: Methacholine vs. ECT

Author Year	Participants enrolled (N); analyzed (N) Age (mean±SD) Males: N (%)	Recruitment Country Index of activity (fitness level)	History of asthma N (%); Asthma severity; Atopic status N (%); History of ICS N (%) History of EIB/EIA	Baseline lung function (FEV_1) Baseline FEV_1 L % predicted
Anderson[23] 2009	510; 375 (performed all tests) 24.3±10.2; range 6-50 182 (48.2)	Clinic (referred for investigation of asthma-type symptoms) U.S. NR	Suspected asthma at ≥step 1 NAEPPII asthma severity grading; mild to stable NAEPPII score 1.2±0.5 293 (78) none within 4 wk prior to study NR	3.32±0.82 L 93.6%±10%
Avital[24] 1989	70; 70 11.3; range 5-19 NR	NR Israel NR	Severe=14; moderate=22; mild=34 NR NR NR	NR NR
Avital[25] 2000	135; 128 12.4±3.9; range 6-25 NR	Clinic (pediatric pulmonology) Israel NR	ATS criteria; mild=85 (63.0), moderate=50 (37.0) NR 38 (28.1) inhaled beclomethasone dipropionate NR	NR 86.1±10.1% All but 4 were above 70% predicted, these 4 had mean FEV_1 65.8±3.9% predicted
Chatham[26] 1982	25; 25 All: 26.4±4.7, asthmatics: 26.5±4.6 All: 15 (60), asthmatics: 9 (60)	Clinic and newspaper advertising U.S. NR	15 (60); mild (all asymptomatic) 15 (60) 12/15 (80); none for 4 wk History of EIA in asthmatics 11/15 (73.3)	NR All: 78.0±3.0%; asthmatics: 76.6±2.7%
Clough[27] 1991	60; 60 Range 7-8 38 (63.3)	Clinic (all registered to 86 general practitioner offices were sent questionnaire) United Kingdom NR	24 (40) physician Dx or receiving anti-asthma med or parent thought child had asthma NR All taking beta-agonists: 21 inhalation, 3 orally; 3 SCG; 1 oral theophylline Atopy 30 (50); ICS 2 (3.3) NR	NR NR

ATS = American Thoracic Society; BHR = bronchial hyper-responsiveness; CI = confidence interval; d = day(s); Dx = diagnosis; ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; hr = hour(s); Hx = history; ICS = inhaled corticosteroids; L = liters; MCH = methacholine; NAEPPII = National Asthma Education and Prevention Program; NR = not reported; prn = as needed; SABA = short-acting beta-agonist; SCG = sodium cromoglycate; SD = standard deviation; Tx = treatment; wk = week(s)

Table 10. Description of participants in the diagnostic test accuracy review: Methacholine vs. ECT (continued)

Author Year	Participants enrolled (N); analyzed (N) Age (mean±SD) Males: N (%)	Recruitment Country Index of activity (fitness level)	History of asthma N (%); Asthma severity; Atopic status N (%); History of ICS History of EIB/EIA	Baseline lung function (FEV_1) Baseline FEV_1 (% predicted)
Eggleston[28] 1979	45; 45 21.1±3.1; range 16-30 27 (60)	NR U.S. NR	45 (100) defined by ATS; NR 42 (93.3) 5 (11.1) Most had history of EIA	NR 94.6±3.9%
Foresi[29] 1986	25; 25 12.5±2.8; range 9-19 19(76)	NR Italy NR	25 (100) clinical Hx of asthma; all FEV_1 >70% predicted, all stable in previous month; 25 (100) none on ICS NR	NR 91.9±9.1%
Henriksen[30] 2002	74; 58 mean 17.9 (95% CI: 17.6, 18.3) 16 (25.4)	Adolescents with wheeze from previous phase of study Norway Physical activity hr/wk, mean (95% CI)=3.1 (2.8-3.5)	NR; beta-agonist=11(19) NR ICS=4(6.6) NR	NR Mean (95% CI)=104(100-107)
Kiviloog[31] 1973	57; 57 31; range 15-61 26(45.6)	Clinic (lung clinic outpatients) Sweden NR	57 (100) defined by ATS, NR extrinsic asthma 32 (56.1%) NR 47 (82.5%)	NR NR
Koh[32] 1996	56; 53 9.9±2.5; range 6-15 41(73.2)	NR South Korea NR	53 (100); mild, stable; beta-agonist prn, SCG 11/56 43 (76.8) NR NR	NR 97.7±13.6% (all ≥70% predicted)
Lin[33] 1991	42 (22 asymptomatic asthma, 20 matched controls); 22 (only asthma pts analyzed) Range 20-40 12(60)	Authors selected subjects China NR	22 asthma patients; stable medicated NR NR NR	Before MCH=2.99±0.48 L, before ECT=2.97±0.45 L NR

Table 10. Description of participants in the diagnostic test accuracy review: Methacholine vs. ECT (continued)

Author Year	Participants enrolled (N); analyzed (N) Age (mean±SD) Males: N (%)	Recruitment Country Index of activity (fitness level)	History of asthma N (%); Asthma severity; Atopic status N (%); History of ICS History of EIB/EIA	Baseline lung function (FEV_1) Baseline FEV_1 % predicted
Pedersen[34] 2008	21; 16 18.3±2.7 0	Elite swimmers (invited to participate) Denmark Athletic (4+ d per wk activity); elite swimmers 22.2±4 hr/wk	None 1 (6.3) NA NR	4.34±0.57 L 110.8±14.6%
Sekerel[35] 1997	12; 12 9.83±1.8 7(58.3)	Clinic (allergy outpatient) Turkey NR	12 (100) confirmed by ATS criteria; stable, varying severity NR 6 (50) Baseline EIB median fall FEV_1=22% (range 4.0–35.0)	NR NR
Souza[36] 2005	43; 30 11±3; range 6-15 14 (46.7)	Clinic (pulmonary outpatient) Brazil NR	Hx of ≥2 episodes dyspnea and/or wheezing relieved with bronchodilators; other Dx ruled out; stable at testing NR None NR	2.39±0.7 L 98±12 %
Verges[37] 2005	39=competitive athletes, 13=controls Athletes=22.4±4.8, controls=27±7 Athletes=26(66.7), controls=7(53.8)	Competitive athletes and healthy sedentary subjects France 13 <2 hr physical activity per wk, 39 >12 hr/wk during 4 mo preceeding study	NR; NR none had allergic asthma ICS: 2 athletes EIB: 4 athletes	Athletes=4.3±7.5 L, controls=4.24±1.08 L Athletes=106.0±12.1%, controls=110±19%

Table 11. Methodological quality of studies in the diagnostic test accuracy review: Methacholine vs. ECT

Author Year	Representative spectrum	Selection criteria defined	Acceptable reference standard	Timing bias avoided	Partial verification avoided	Differential verification avoided	Clear reporting of index test	Clear reporting of reference standard	Index test blinded	Reference standard blinded	Uninterpretable results reported	Withdrawals explained
Anderson[23] 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Avital[24] 1989	U	No	U	U	Yes	Yes	No	No	U	U	U	Yes
Avital[25] 2000	U	U	Yes	No	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Chatham[26] 1982	No	U	Yes	Yes	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Clough[27] 1991	U	U	Yes	Yes	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Eggleston[28] 1979	U	No	Yes	U	Yes	Yes	Yes	U	U	U	U	Yes
Foresi[29] 1986	U	U	Yes	Yes	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Henriksen[30] 2002	No	No	Yes	Yes	U	U	U	Yes	U	U	No	No
Kiviloog[31] 1973	U	No	Yes	No	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Koh[32] 1996	U	No	U	U	Yes	Yes	Yes	Yes	U	U	U	Yes
Lin[33] 1991	No	No	Yes	Yes	U	U	Yes	U	U	U	Yes	No
Pedersen[34] 2008	No	No	U	Yes	Yes	Yes	Yes	U	U	U	Yes	Yes
Sekerel[35] 1997	U	U	U	Yes	Yes	Yes	Yes	U	U	U	Yes	Yes
De Souza[36] 2005	U	No	Yes	Yes	U	Yes	Yes	Yes	U	U	U	Yes
Verges[37] 2005	U	No	U	No	Yes	Yes	Yes	Yes	U	U	Yes	Yes

U = unclear

Key Question D–3: Sport or Venue Specific Exercise Challenges

Description of Included Studies

Five studies[34,38-41] met the inclusion criteria for the diagnostic test accuracy review of sport or venue specific exercise challenges compared with a standardized exercise challenge test (ECT). Three studies focused on swimming challenges,[34,38,40] one assessed short track speed skating and biathlon field challenges,[39] and one assessed five cold weather sport challenges.[41] Tables 12 and 13 summarize the study and participant characteristics.

Dickinson et al.[39] included elite winter athletes who were members of Great Britain's national teams for short track speed skating (n=10) and biathlon (n=4). The sport specific challenge for speed skaters involved indoor skating for 6 minutes at an 11 to 12 second pace per 250 meter lap. The sport specific challenge for biathletes was a 20 minute simulated race in Finland. The standardized ECT was performed on a treadmill for 8 minutes; the intensity level was more than 90 percent of maximum heart rate for the final 4 minutes. As part of this study, participants also completed an EVH challenge test (see Key Question D-4 for details). Two (14 percent) participants had a previous diagnosis of asthma and were taking asthma medication. Rundell et al.[41] included 23 elite winter athletes who competed in a race or race simulation at their regular sport (biathlon, short-track speed skating, Nordic combined, cross country skiing, or kayaking) and demonstrated a drop in FEV_1 of 10 percent or more. Seven of the participants had been diagnosed with EIA as children but took no medications at the time of the study.

Castricum et al.[38] included 33 elite swimmers who were members of Australia's state, national or international teams. The swim challenge required participants to swim for 8 minutes at more than 85 percent of their predicted maximum heart rate in an indoor 50 meter pool. The standardized ECT was a bicycle ergometer test; participants cycled at more than 90 percent of their predicted maximum heart rate. As part of this study, participants also completed an EVH challenge test (see Key Question D-4 for details). Thirteen (39 percent) participants had a previous diagnosis of asthma; of these, 11 were taking asthma medication.

In the study by Pedersen et al.[34] 16 elite (national or international caliber) female swimmers from Denmark underwent four different challenge tests: swimming, MCH, EVH, and a standardized ECT performed on a treadmill (see also Key Questions D-2 and D-4). The swim challenge was carried out under race conditions at the National Danish Swimming Championships. The distances were 200 meters (n=11), 400 meters (n=3) and 800 meters (n=2). For the treadmill test, the participants were instructed to run until exhaustion. None of the swimmers had a previous diagnosis of asthma.

Reggiani et al.[40] assessed nine competitive swimmers from Italy; all had been involved in competitive swimming for at least 5 years. The swim challenge required participants to swim for 8 minutes at 80 percent of their maximum heart rate in an indoor 25 meter pool. The standardized ECT was a bicycle ergometer test; participants cycled at 80 percent of their maximum heart rate for 8 minutes. As part of this study, participants also completed a FRAST (see Key Question D-5 for details). All participants had a history of atopic diseases; they were asymptomatic at the time of the challenge tests.

Methodological Quality of the Included Studies

Table 14 summarizes the methodological quality of the included studies. There are several methodological issues. None had a representative patient spectrum which suggests the possibility of spectrum bias. Blinding of assessment of the ECT to the results of the index test was not reported. Two studies[38,40] did not report their source of funding; one reported industry funding;[39] one was supported by government grants,[34] and one by the United States Olympic Committee.[41] The body of evidence is classified as "low."

Quantitative Results

In the study by Dickinson et al.[39] three (21 percent) athletes had a positive test on the sport specific challenge using a FEV_1 fall index of 10 percent or more. None of the participants had a positive test on the ECT; therefore, sensitivity could not be calculated. Specificity of the sport specific challenge was 79 percent (95 percent CI: 49, 95) indicating an 80 percent probability that for participants who do not have EIB/EIA, the sport challenge would correctly identify them as not having EIB/EIA. All of the athletes in the study by Rundell et al.[41] were positive on a sport specific challenge. Five were also positive on an ECT at 95 percent of peak heart rate for 8 minutes. Sensitivity was 100 percent (95 percent CI: 48, 100). Overall, 5 (14 percent) of the cold weather athletes were positive for EIB/EIA on the ECT; 21 (57 percent) were positive for EIB/EIA on cold air challenges. None of the participants had a negative test on the sport specific challenge.

The sensitivity of the swimming challenge tests ranged from 0[40] to 50 percent[34] (Figure 7). The specificity ranged from 83 to 100 percent. Overall, 11 (19 percent) of the swimmers were positive for EIB/EIA on the ECT; 5 (9 percent) were positive for EIB/EIA on the swimming challenge.

Figure 7. Forest plot of sensitivity and specificity: Sport specific challenges vs. ECT (FEV_1 fall index 10 percent or more)

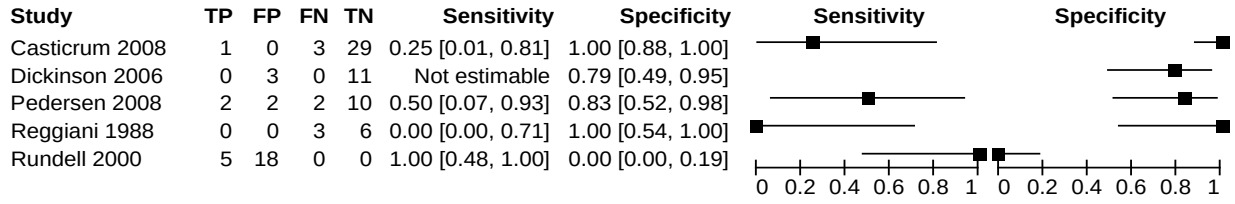


Table 12. Description of studies in the diagnostic test accuracy review: Sport specific vs. ECT

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (min) Load; Environmental conditions Follow-up time points Author definition of EIB	INDEX TEST (Sport specifc challenge) Type; Description Follow-up time points Author definition of EIB
Castricum[38] 2008	Cross sectional (prospective); randomized order of tests 3; 1; between 1 and 7 d Asthma med withheld for designated time	Bicycle ergometer; 8 91±4.8% max HR; RH 60.5±2.1%; 21±0.8°C 1, 3, 5, 7, 10 min post ECT ≥10% fall FEV_1	Swimming: 50 m chlorine and ozone filtered indoor pool; temp: 30±2.7°C; pool temp: 27±0.3°C; RH: 82±4.58%; swim x 8 min to maintain >85% max HR 1, 3, 5, 7, 10 min post challenge ≥10% fall FEV_1
Dickinson[39] 2006	Cross sectional (prospective); randomized order of tests NR Asthma med withheld: ICS and LABA x 3 d; SABA x 1 d	Treadmill; 8 90% max HR; RH 56%; 18°C 3, 5, 10, 15 min post ECT ≥10% fall FEV_1	Skating: indoor speed skating rink; 8°C, RH 35%; 6 min, Biathlon: simulated outdoor race x 20 min; temp 1-2°C; RH 31-34% 3, 5, 10, 15 min post challenge ≥10% fall FEV_1
Pedersen[34] 2008	Cross sectional (prospective); NR 4 visits; NR; at least 24 hr apart NA	Treadmill: constant speed, incline increased every 2 min; 5±1.1 min; ran to exhaustion; RH and temp NR 0, 1, 3, 5, 10, 15, 20 min post ECT ≥10% fall FEV_1	Swimming: Race conditions at national championships; swimmers chose favorite distance from 200 m to 800 m; 2 min at highest possible speed; temp and RH NR 1, 3, 5, 10, 15, 20 min post challenge ≥10% fall FEV_1
Reggiani[40] 1988	Cross sectional (prospective); NR 3; 1; ≥3 d to <1 wk None on ICS	Bicycle ergometer; 8 80% max HR; RH 76%; 22°C, in environmental chamber 5, 10, 15, min post ECT ≥20% fall FEV_1	Swimming: 25 m indoor pool, pool temp 26°C; 8 min at 80% max HR 5, 10, 15 min post challenge ≥20% fall FEV_1
Rundell 2000	Cross sectional (prospective); Sport specific first 2; 1 Different days None on asthma med	Treadmill: 8 (no warmup) 95% peak HR RH 60%; 21°C 5, 10, 15, min post ECT ≥10% fall FEV_1	Biathlon, short-track speed skating, cross country skiing, Nordic combined, kyaking**:** followed usual warmup routine then performed in competition; duration from 1 min 20 sec for speed skaters to >1h for cross country skiers 5, 10, 15 min post competition ≥10% fall FEV_1

C = Celsius; d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; hr = hour(s); HR = heart rate; ICS = inhaled corticosteroids; LABA = long-acting beta-agonist; m = meters; max = maximum; med = medication(s); min = minute(s); NA = not applicable; NR = not reported; RH = relative humidity; SABA = short-acting beta-agonist; temp = temperature; wk = week(s)

Table 13. Description of participants in the diagnostic test accuracy review: Sport specific vs. ECT

Author Year	Participants enrolled (N); analyzed (N) Age (mean±SD) Males: N (%)	Recruitment Country Index of activity (fitness level)	History of asthma N (%); Asthma severity; Atopic status N (%); History of ICS History of EIB/EIA	Baseline lung function (FEV_1) Baseline FEV_1 % predicted
Castricum[38] 2008	33; 33 18.2±4.9 23 (69.7)	Competative athletes (swimmers; volunteers) Australia Athletic	13 (39.4); NR NR 3 ICS; 3 ICS+LABA; 1 MSC; 4 SABA prn; 2 no med; No	4.45±0.86 L 114.73±14.97%
Dickinson[39] 2006	14; 14 22.6±5.7 NR	Competative athletes (speed skating, biathalon; volunteers) United Kingdom Athletic	2 (14); NR NR 2 (14) ICS or SABA No	4.4±0.4 L 105±11.8%
Pedersen[34] 2008	21; 16; 18.3±2.7; range 15–25 0	Competative athletes (swimmers; invited) Denmark Athletic (4+ days per wk activity); elite swimmers 22.2±4 hr/wk	None 1 (6.3) NA NR	4.34±0.57 L 110.8±14.6%
Reggiani[40] 1988	9; 9 15.1±2.0 7 (77.8)	Competitive athletes (swimmers; volunteers) Italy Athletic average 40 km/wk	NR; stable and asymptomatic at testing 9 (100) NR NR	4.18±1.16 L NR
Rundell[41] 2000	23; 23 20.0±4.5 14 (61)	Competitive athletes (biathlon, short-track speed skating, cross-country skiing, Nordic combined, kyaking; invited) United States Elite cold weather athletes	7 (30) EIA as children; NR None on oral/inhaled med 23 (100)	4.76±1.0 L All >100%

Dx = diagnosis; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; hr = hour(s); Hx = history; ICS = inhaled corticosteroids; km = kilometers; LABA = long-acting beta-agonist; L = liters; MCS= mast cell stabilizers; NA = not applicable; NR = not reported; prn = as needed; SABA = short-acting beta-agonist; SD = standard deviation; wk = week(s)

Table 14. Methodological quality of studies in the diagnostic test accuracy review: Sport specific vs. ECT

Author Year	Representative spectrum	Selection criteria defined	Acceptable reference standard	Timing bias avoided	Partial verification avoided	Differential verification avoided	Clear reporting of index test	Clear reporting of reference standard	Index test blinded	Reference standard blinded	Uninterpretable results reported	Withdrawals explained
Castricum[38] 2008	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Dickinson[39] 2006	No	No	Yes	U	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Pedersen[34] 2008	No	No	U	Yes	Yes	Yes	Yes	U	U	U	Yes	Yes
Reggiani[40] 1988	No	U	Yes	Yes	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Rundell[41] 2000	No	U	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes

U = unclear

Key Question D–4: Eucapnic Voluntary Hyperpnea

Description of Included Studies

Seven studies[34,38,39,42-45] met the inclusion criteria for the diagnostic test accuracy review of eucapnic voluntary hyperpnea (EVH) compared with a standardized ECT. All seven studies were conducted prospectively. Six [34,38,39,43-45] used a cross sectional design, and one[42] used a case-control design with healthy controls. They were all published in peer reviewed journals. The median year of publication was 2005 and ranged from 1984 to 2008. Studies were conducted in Europe,[34,39,45] Australia,[38] and the United States.[42-44]

The characteristics of the studies are summarized in Table 15. The standardized ECT was performed on a treadmill[34,39,43,45] or a bicycle ergometer.[38,42,44] A positive test was defined as a FEV_1 fall index of 10 percent or more,[34,38,39,44] or 15 percent or more.[45] Two studies did not report their definitions of a positive ECT.[42,43] The target workload was reported as 90 percent of maximum heart rate,[38,39] pulse rate of greater than 170 after 2 minutes of running (equivalent to 80 percent of predicted maximum heart rate),[45] "until exhaustion,"[34] "until a symptom limited maximum exercise capacity,"[42] and "highest intensity."[44] One study[43] did not report the criteria for target workload.

Most studies used five percent CO_2 air content for the EVH challenge at room temperature. One study[42] also tested participants with cold air. The duration of hyperpnea was either 5 minutes[42] or 6 minutes.[34,38,39,44,45] One study[43] did not report duration. During the EVH challenge, the target ventilation rate was set at 80 percent maximum voluntary ventilation (MVV),[42] 85 percent MVV,[38,44] a minimum ventilation of 30 times FEV_1 equivalent to MVV,[34] or 40 or more liters per minute.[43] Two studies[39,45] did not specify the rate of target ventilation.

The baseline characteristics of the participants are presented in Table 16. The number of participants in each study ranged from 10 to 33. Three studies included adults only,[39,42,44]one included children only,[45] two included both adults and children,[34,38] and one[43] did not report the age of participants. Four studies[34,38,39,44] focused on elite athletes; three[42,43,45] did not report the level of fitness or sports participation. Fourteen[39] to 100 percent of participants[43,45] had a diagnosis of asthma in the five studies that reported this. In three studies[43-45] 100 percent of participants had a history of EIB/EIA.

Methodological Quality of Included Studies

Table 17 summarizes the methodological quality of the included studies. As a group, there are methodological issues that limit interpretation and generalizability of the results. Of concern is the risk of spectrum bias in all studies. Either the participants recruited into the studies were volunteers,[34,38,39,42,44] or the recruitment source and methods were not reported.[43,45] In some studies all participants had a history of EIB/EIA[43-45] and therefore are not representative of the spectrum of patients who might be tested for EIB/EIA. Blinding of results of the ECT to the results of the EVH challenge was not reported. Four studies did not report their sources of funding.[38,42,43,45] Two studies received funding support from industry,[39,44] and one was supported by government and institution grants.[34] The body of evidence is classified as "low."

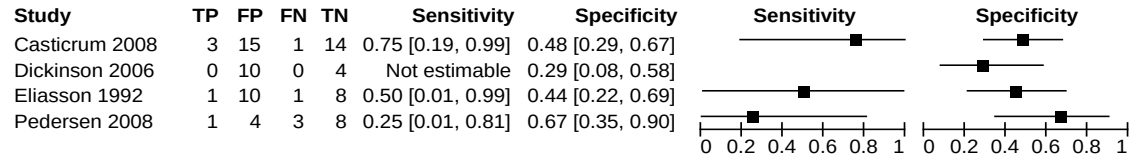
Quantitative Results

A total of 138 participants were studied; 42 (30 percent) tested positive for EIB/EIA on the ECT and 74 (54 percent) were positive using EVH. Overall, the sensitivity and specificity of the

seven studies were heterogeneous with values ranging from 25 to 90 percent for sensitivity and 0 to 71 percent for specificity (data not shown).

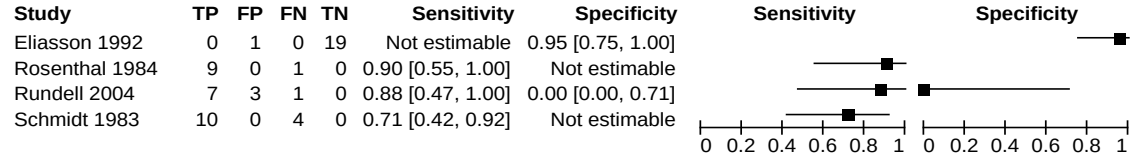
To explore the heterogeneity, we conducted a post hoc subgroup analysis of participants who did not have a history of EIB/EIA. This included all participants from three studies[34,38,39] and one group of participants from a fourth study.[42] Among these 83 individuals, 10 (12 percent) tested positive on the ECT while 44 (53 percent) tested positive using EVH. Heterogeneity was somewhat reduced and the range of sensitivity and specificity was narrowed—25 to 75 percent and 29 to 67 percent, respectively (Figure 8). Of note, the studies by Castricum et al.,[38] Dickinson et al.,[39] and Pedersen et al.[34] focused on elite athletes (proportion with asthma 39, 14 and 0 percent, respectively).

Figure 8. Forest plot of sensitivity and specificity: Eucapnic voluntary hyperpnea vs. ECT (participants with no history of EIB/EIA; FEV_1 fall index 10 percent or more for ECT and EVH)



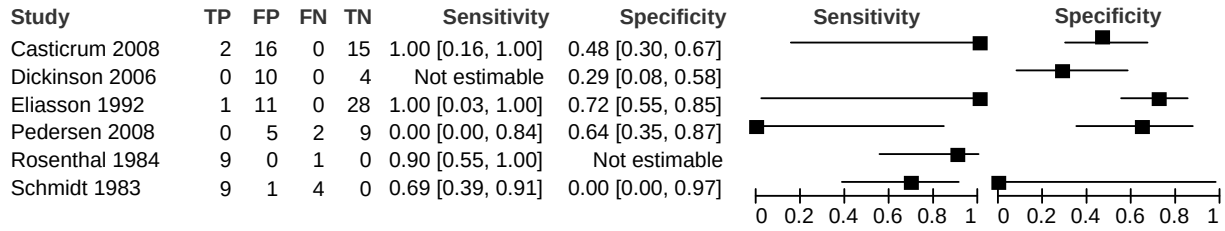
For the three studies[43-45] and one group[42] in which all participants had a history of EIB/EIA the sensitivity of EVH was higher, ranging from 71 to 90 percent[43] (Figure 9). Among these 55 people, 32 (58 percent) tested positive for EIB/EIA using the ECT and 30 (55 percent) tested positive using EVH.

Figure 9. Forest plot of sensitivity and specificity: Eucapnic voluntary hyperpnea vs. ECT (participants with a history of EIB/EIA; FEV_1 fall index 10 percent or more for ECT and EVH)



Subgroup and sensitivity analyses. Sensitivity analyses were performed using different thresholds for a positive EVH challenge. Using a threshold of a FEV_1 fall index of 15 percent or more for a positive EVH challenge, the sensitivity improved; however, there was still considerable heterogeneity (Figure 10). The results of the analyses using a threshold of 20 percent or more were not substantially different (data not shown). In a subgroup analysis on studies enrolling athletes the sensitivity ranged 25 to 88 percent; specificity ranged 0 to 67 percent (data not shown).

Figure 10. Forest plot of sensitivity and specificity: Eucapnic voluntary hyperpnea vs. ECT (all participants; threshold for a positive test is a FEV_1 fall index 10 percent or more for ECT and 15 percent or more for EVH)



Cold air versus warm air. In the study by Eliasson et al.[42] participants performed EVH tests while inspiring air at room temperature or inspiring air cooled to minus 18°C to minus 26°C. Despite the increased conditioning of the air required during the cold air trial, there was no difference in post-EVH FEV_1 response between the cold versus room temperature challenges (data not shown).

Table 15. Description of studies in the diagnostic test accuracy review: Eucapnic voluntary hyperpnea vs. ECT

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (min) Load; Environmental conditions Follow-up time points Author definition of EIB	INDEX TEST (EVH) Type; Description Follow-up time points Author definition of EIB
Castricum[38] 2008	Cross sectional (prospective); randomized order of tests 3; 1; between 1 and 7 d Asthma med withheld	Bicycle ergometer; 8 91±4.8% max HR RH 60.5±2.1%, 21±0.8°C 1, 3, 5, 7, 10 min post ECT ≥10% fall FEV_1	Gas (dry) 5% CO_2, 21% O_2, 74% N_2; 21±0.8°C, RH 60.5±2.1%; Load=85% MVV x 6 min 1, 3, 5, 7, 10 min post challenge ≥10% fall FEV_1
Dickinson[39] 2006	Cross sectional (prospective); randomized order of tests NR Asthma med withheld before tests (ICS x 3 d; LABA x 2 d, SABA x 1 d)	Treadmill; 8 90% max HR RH 56%, 18°C 3, 5, 10, 15 min post ECT ≥10% fall FEV_1	Gas (dry) 5% CO_2, 21% O_2, N_2, 74%; 19.1°C, RH <2%; Load: hyperventilate x 6 min 1, 3, 5, 7, 10 min post challenge ≥10% fall FEV_1
Eliasson[42] 1992	Case-control (prospective); randomized order of tests At least 4; 1; all challenges between 7-9 am No caffine x 12 hr prior to tests SABA/LABA discontinued	Bicycle ergometer at 60 rpm with resistance increased by 25 watts/min; NR Symptom-limited max exercise capacity ambient indoor conditions 0, 5, 10, 15 min post ECT NR	1) Gas (dry) compressed air 5% CO_2 x 5 min at 80% MVV; 2) Gas (cold air, -18 to -26°C) 5% CO_2 x 5 min at 80% MVV 1 then 5 min intervals for 15 min post challenge NR
Pedersen[34] 2008	Cross sectional (prospective); NR 4 visits; NR; at least 24 hr apart NA	Treadmill at constant speed; incline increased 2% every 2 min; 5±1.1 until exhaustion NR 0, 1, 3, 5, 10, 15, 20 min post ECT ≥10% fall FEV_1	Gas (dry) 5% CO_2, 21% O_2, 74% N_2; room temp x 6 min; Load: 85% MVV 0, 1, 3, 5, 10, 15, 20 min post challenge ≥10% fall FEV_1
Rosenthal[43] 1984	Cross sectional (prospective); NR 2; 1; >24 hr otherwise unspecified NR	Treadmill; NR; NR dry air, room temperature NR NR	Gas (dry) 5% $C0_2$, 21% O_2, 74% N_2; room temp; Load: hyperventilate at ≥40 L/min NR NR
Rundell[44] 2005	Cross sectional (prospective); randomized order of tests 4; 1; 48-72 hr NR	Bicycle ergometer; 6 Highest intensity RH 50%, -3°C 5, 10, 15 min post ECT ≥10% fall FEV_1	Gas (dry) 5% CO_2, 21% O_2, 74% N_2; 21°C, RH 40%; Load: 85% MVV 5, 10, 15 min post challenge ≥10% fall FEV_1

bpm = beats per minute; C = Celsius; d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; hr = hour(s); HR = heart rate; ICS = inhaled corticosteroids; L/min = liters per minute; LABA = long-acting beta-agonist; m = meters; µmol = micromole; max = maximum; med = medication(s); mg/ml = milligram per milliliter; min = minute(s); MMV = maximal voluntary ventilation; NR = not reported; RH = relative humidity; PEF = peak expiratory flow; rpm = revolutions per minute; SABA = short-acting beta-agonist; temp = temperature

Table 15. Description of studies in the diagnostic test accuracy review: Eucapnic voluntary hyperpnea vs. ECT (continued)

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (min) Load; Environmental conditions Follow-up time points Author definition of EIB	INDEX TEST (EVH) Type; Description Follow-up time points Author definition of EIB
Schmidt[45] 1983	Cross sectional (prospective); randomized order of tests 2; 1; 24 hr All med x 8 hr prior to tests	Treadmill; 6; HR >170 bpm after 2 min running (~80% max HR) RH 40%, 21°C 0, 1, 3, 5, 10, 15 min post ECT ≥15% fall in PEF	Gas 5% CO_2, 21% O_2, 74% N_2; 21°C, RH 40% ; Load: hyperventilate vigorously x 6 min NR >15% fall in PEF from baseline

Table 16. Description of participants in the diagnostic test accuracy review: Eucapnic voluntary hyperpnea vs. ECT

Author Year	Participants enrolled (N); analyzed (N) Age (mean±SD) Males: N (%)	Recruitment Country Index of activity (fitness level)	History of asthma N (%); Asthma severity; Atopic status N (%) History of ICS History of EIB/EIA	Baseline lung function (FEV_1) Baseline FEV_1 % predicted
Castricum[38] 2008	33; 33 18.2±4.9 23 (69.7)	Athlete volunteers at state level or above Australia Athletic	13 (39.4); NR NR 3 ICS; 3 ICS+LABA; 1 mast; 4 SABA as needed; 2 no med NR	4.45±0.86 L 114.73±14.97%
Dickinson[39] 2006	14; 14 22.6±5.7 NR	Athlete volunteers from Great Britain short track speed skating and biathlon teams United Kingdom Athletic	2 (14) Hx of asthma; NR NR 2 (14) treated with ICS or SABA NR	4.4±0.4 L 105±11.8%
Eliasson[42] 1992	40; 40 Range 22–42 33 (82.5)	Clinic (from pulmonary clinic with suspected EIB; healthy controls with no symptoms of EIB), volunteers U.S. NR	9 (23) family Hx of asthma; NR; 20 (50) self-report: post-exercise wheeze=13; dyspnea out of proportion to level of exertion=11; chest tightness=8 16 (40) seasonal allergies; 5 (13) food allergies None on ICS or NSAIDs 20 had EIB; 20 did not	NR EIB=100.1±11.7% Control=104.5±9.8%
Pedersen[34] 2008	21; 16 18.3±2.7 0	Athletic team of elite swimmers (invited to participate) Denmark Athletic (4+ d/wk activity), elite swimmers 22.2±4 hr/wk	None; NA 1 (6.3) NA NR	4.34±0.57 L 110.8±14.6%
Rosenthal[43] 1984	10; 10 NR NR	NR U.S. NR	10 (100); NR NR NR 10 (100)	NR NR
Rundell[44] 2005	11; 11 22.8±6.8 8 (72.7)	11 volunteers, EIB positive, recreational and college athletes U.S. Athletic	4 (36); 4 mild NR NR 11 (100)	4.0±0.75 L 98.4±14.2%
Schmidt[45] 1983	14; 14 11.6; range 8-14 NR	NR Denmark NR	14 (100); NR NR NR 14 (100)	NR NR

Dx = diagnosis; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; Hx = history; ICS = inhaled corticosteroids; LABA = long-acting beta-agonist; L = liters; med = medication(s); min = minute(s); NA = not applicable; NSAID=non-steroidal anti-inflammatory; NR = not reported; PEF = peak expiratory flow; SABA = short-acting beta-agonist; SD = standard deviation; wk = week(s); y = year

Table 17. Methodological quality of studies in the diagnostic test accuracy review: Eucapnic voluntary hyperpnea vs. ECT

Author Year	Representative spectrum	Selection criteria defined	Acceptable reference standard	Timing bias avoided	Partial verification avoided	Differential verification avoided	Clear reporting of index test	Clear reporting of reference standard	Index test blinded	Reference standard blinded	Uninterpretable results reported	Withdrawals explained
Castricum[38] 2008	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Dickinson[39] 2006	No	No	Yes	U	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Eliasson[42] 1992	U	Yes	U	Yes	Yes	Yes	U	Yes	U	U	Yes	Yes
Pedersen[34] 2008	No	No	U	Yes	Yes	Yes	Yes	U	U	U	Yes	Yes
Rosenthal[43] 1984	No	No	U	Yes	Yes	Yes	No	No	U	U	Yes	Yes
Rundell[44] 2005	No	No	U	Yes	Yes	Yes	Yes	U	U	U	Yes	Yes
Schmidt[45] 1983	No	No	U	Yes	Yes	Yes	Yes	Yes	U	U	Yes	Yes

U = Unclear

Key Question D–5: Free Running Asthma Screening Test

Description of Included Studies

Three studies[36,40,46] met the inclusion criteria for the diagnostic test accuracy review of a free running asthma screening test (FRAST) compared with a standardized exercise challenge test (ECT). All studies were conducted prospectively; two used a cross sectional design[36,40] and one used a case-control design with healthy controls.[46] The studies were published in peer reviewed journals in 1988,[40] 2005[36] and 2008.[46] The studies were conducted in Europe[40,46] and South America.[36]

The standardized ECT was performed on a treadmill[46] and a bicycle ergometer.[36,40] All free running tests took place indoors. Garcia de la Rubia et al.[46] defined a positive test as a FEV_1 fall index of 20 percent or more on the treadmill and a 16.5 percent or more for the FRAST. Among children with asthma the maximum heart rate ranged from 70 to 90 percent in treadmill running and 82 to 93 percent in free running. Results were not reported for the control group. Reggiani et al.[40] defined a positive test as a FEV_1 fall index of 20 percent or greater on the bicycle ergometer and the FRAST. The target workload was 80 percent of maximum heart rate for both tests. As part of the study the authors also assessed the diagnostic characteristics of a sport specific (swimming) challenge (see Key Question D-3 for details). Souza et al.[36] defined a positive test as a FEV_1 fall index of 10 percent or greater for both the ECT and FRAST. The target workload was between 80 and 90 percent of maximum heart rate for both tests. The characteristics of the studies are summarized in Table 18.

The baseline characteristics of the participants are presented in Table 19. Sixty people were enrolled in the study by Garcia de la Rubia et al.,[46] 30 had extrinsic asthma but were asymptomatic at testing. The 30 healthy controls had never presented with symptoms of asthma and had no history of allergy. The nine competitive swimmers who participated in the study by Reggiani et al.[40] all had a history of atopy but were asymptomatic at the time of testing. In the study by Souza et al.[36] the 30 participants analyzed had intermittent asthma defined as at least two episodes of dyspnea and/or wheezing relieved with the use of bronchodilators.

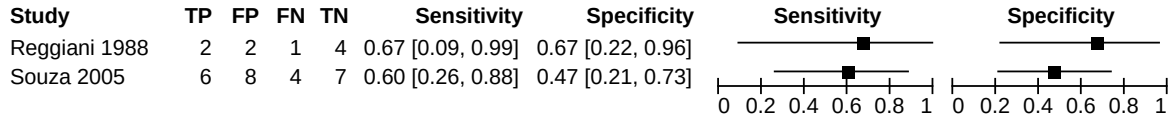
Methodological Quality of the Included Studies

Table 20 summarizes the methodological quality of the included studies. Overall there were concerns with the methodological quality of the studies. Generalizing the results to a target population of people with suspected EIB/EIA may be limited as none of the studies had representative spectrum of participants. Blinding of assessment of the ECT to the results of the FRAST was not reported. None of the studies reported their source of funding. The body of evidence is classified as “very low.”

Quantitative Results

For two studies[36,40] the sensitivity and specificity could be calculated using a FEV_1 fall index of 10 percent or more on both challenges. The sensitivity of FRAST was 60 and 67 percent; specificity was 47 and 67 percent (Figure 11). Overall, 13 (38 percent) participants had a positive ECT; 18 (53 percent) had a positive FRAST.

Figure 11. Forest plot of sensitivity and specificity: FRAST vs. ECT (FEV_1 fall index ≥10%)



Garcia de la Rubia et al.[46] used a FEV_1 fall index of 20 percent or more as the threshold for a positive test for the ECT and 16.5 percent or more for the FRAST. Based on these thresholds the sensitivity was 53 percent (95 percent CI: 34, 72) and the specificity was 100 percent (94 percent CI: 88, 100). Thirty (50 percent) participants had a positive ECT; 16 (27 percent) had a positive FRAST.

Table 18. Description of studies in the diagnostic test accuracy review: FRAST vs. ECT

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (min) Load; Environmental conditions Follow-up time points Author definition of EIB	INDEX TEST (FRAST) Type; Description Follow-up time points Author definition of EIB
Garcia de la Rubia[46] 1998	Case-control (prospective); NR 2; 1; within 7 d NR	Treadmill; 6-8 Variable speed/incline 5%; 70-90% max HR; RH 53.69±5.34%, 19.06±1.39°C 2, 5, 10, 15, 20 min post ECT ≥20% fall FEV_1	Indoor sports center; 6-8 min; 82-93% max HR; RH 54.73±3.41%, 19.96±1.01°C NR ≥16.5% fall FEV_1
Reggiani[40] 1988	Cross sectional (prospective); NR 3; 1; ≥3 d to <1 wk None on ICS	Bicycle ergometer; 8 80% max HR; RH 76%, 22°C; in environmental chamber 5, 10, 15 min post ECT ≥20% fall FEV_1	25 m indoor pool, 8 min at 80% max HR; RH NR; pool temp 26°C; 5, 10, 15 min post challenge; ≥20% fall FEV_1
Souza[36] 2005	Cross sectional (prospective); Randomized order of tests 3; 1 (all 8-10 am); min 24 hr to 10 d None; asthma med stopped based on guidelines	Bicycle ergometer; 6 90-100% max HR; RH 50%, 21.1±1°C, 3, 6, 10, 15, 20, 30 min post ECT ≥10% fall FEV_1	Indoors along 50 m corridor; 6 min; 80-90% max HR; RH 50%, 22±2°C, wore nose clips 3, 6, 10, 15, 20, 30 min post challenge ≥10% fall FEV_1

d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; hr = hour(s); HR = heart rate; ICS = inhaled corticosteroids; m = meters; max = maximum; MCH = methacholine; med = medication(s); mg/ml = milligram per milliliter; min = minute(s); NR = not reported; RH = relative humidity; temp = temperature

Table 19. Description of participants in the diagnostic test accuracy review: FRAST vs. ECT

Author Year	Participants enrolled (N); analyzed (N) Age (mean±SD) Males: N (%)	Recruitment Country Index of activity (fitness level)	History of asthma N (%); Asthma severity; Atopic status N (%); History of ICS History of EIB/EIA	Baseline lung function (FEV_1) Baseline FEV_1 % predicted
Garcia de la Rubia[46] 1998	60; 60 Asthma: 9.8±1.9, Control: 10.7±2.0 NR	University medical sports center Spain NR	Asthma group: 30 (100); stable 30 (100) NR NR	Asthma group: FVC ≥65% predicted NR
Reggiani[40] 1988	9; 9 15.1±2.0 7 (77.8)	Competitive swimmers (volunteers) Italy Athletic average 40 km/wk	NR 9 (100); stable and asymptomatic at testing NR NR	4.18±1.16 L NR
Souza[36] 2005	43; 30 11±3; range 6-15 14 (46.7)	Pulmonary outpatient clinic Brazil NR	30 (100); Intermittant NR 0 (0) NR	2.39±0.7 L 98±12%

EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroids; km/wk = kilometers per week; L = liters; NR = not reported; SD = standard deviation

Table 20. Methodological quality of studies in the diagnostic test accuracy review: FRAST vs. ECT

Author Year	Representative spectrum	Selection criteria defined	Acceptable reference standard	Timing bias avoided	Partial verification avoided	Differential verification avoided	Clear reporting of index test	Clear reporting of reference standard	Index test blinded	Reference standard blinded	Uninterpretable results reported	Withdrawals explained
Garcia de la Rubia[46] 1998	U	No	U	Yes	Yes	Yes	Yes	Yes	U	U	Yes	U
Reggiani[40] 1988	No	U	Yes	Yes	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Souza[36] 2005	U	No	Yes	Yes	U	Yes	Yes	Yes	U	U	U	Yes

U = unclear

Key Question D–6: Mannitol Challenge

Description of Included Studies

Three studies[23,47,52] met the inclusion criteria for the diagnostic test accuracy review of Mannitol compared with a standardized exercise challenge test (ECT). All studies used a cross sectional design and all were conducted prospectively. The characteristics of the studies and the participants are summarized in Tables 21 and 22.

In the study by Anderson et al.[23] the standardized ECT was performed on a treadmill. The target workload was between 80 and 90 percent of maximum heart rate. A positive test was defined as a FEV_1 fall index of 10 percent or greater. A positive test for the mannitol challenge was defined as a FEV_1 fall index of 15 percent or more or a fall of 10 percent or more between consecutive doses. As part of the study the authors also compared the ECT to a MCH challenge (See Key Question D-2). In total, there were 510 participants enrolled, 375 underwent all three challenge tests and were included in the final analyses. Both children (26 percent) and adults (74 percent) were included in the study. Participants had symptoms suggestive of asthma but none had a confirmed diagnosis. Symptoms suggested mild, persistent asthma (i.e., symptoms two or more times per week; asymptomatic between exacerbations; exacerbations of only a few hours to a few days; night time symptoms two or more times per month).[109] Seventy-eight percent of participants were atopic.

Brannan et al.[47] used a standardized bicycle ergometer challenge. The target workload was between 90 and 100 percent of maximum heart rate. A positive test was defined as a FEV_1 fall index of 10 percent or greater. A positive test for the mannitol challenge was defined as a FEV_1 fall index of 15 percent or more. As part of the study the authors also compared the ECT to an EVH challenge (See Key Question D-4). In total 36 adults were enrolled in the study; however, only 23 (64 percent) completed both the mannitol challenge and the ECT. All participants had atopic asthma, were taking asthma medications, and had a self-reported history of EIA.

In the study by Kersten et al.[52] the ECT was performed on a treadmill. The target workload was approximately 90 percent of predicted maximum heart rate for 6 minutes. A positive test for both the ECT and the mannitol challenge was defined as a FEV_1 fall index of 15 percent or greater. In total, 33 children were enrolled; 25 underwent both challenge tests and were included in the final analyses. All children had a history of allergic asthma and EIA.

Methodological Quality of Included Studies

Table 23 summarizes the methodological quality of the three studies. Of concern is the risk of spectrum bias in the studies by Brannan et al.[47] and Kersten et al.[52] Participants were volunteers who had a history of EIA and are not representative of the spectrum of patients who might be tested for EIB/EIA. Blinding of the results of the ECT and the index test was not reported. There were no details about uninterpretable or indeterminate index test results in two of the three trials. All studies reported their sources of funding: Anderson et al.[23] received funding support from industry; Brannan et al.[47] and Kersten et al.[52] were supported by government grants. The body of evidence is classified as “moderate.”

Quantitative Results

Using the threshold of a FEV_1 fall index of 10 percent or more for the ECT, 23 (100 percent) participants in the Brannan et al.[47] study were diagnosed with EIA; 22 (96 percent) were positive

on the mannitol challenge. The sensitivity was 96 percent (95 percent CI: 78, 100). Specificity could not be calculated as none of the participants tested negative on the ECT (Figure 12).

Anderson et al.[23] reported a sensitivity of 58 percent (95 percent CI: 50, 66) and a specificity of 65 percent (95 percent CI: 58, 72) (Figure 12). The ECT diagnosed 163 (44 percent) participants with EIA; 168 (45 percent) were positive on the mannitol challenge.

In the study by Kersten et al.[52] sensitivity was 69 percent (95 percent CI: 41, 89) and specificity was 78 percent (95 percent CI: 40, 97) (Figure 12). The ECT diagnosed 16 (64 percent) participants with EIA; 13 (52 percent) were positive on the mannitol challenge. Three participants had to terminate the mannitol challenge due to persistent cough and were excluded from analysis.

Figure 12. Forest plot of sensitivity and specificity: Mannitol vs. ECT (FEV_1 fall index ≥10% for ECT and ≥15% for mannitol)

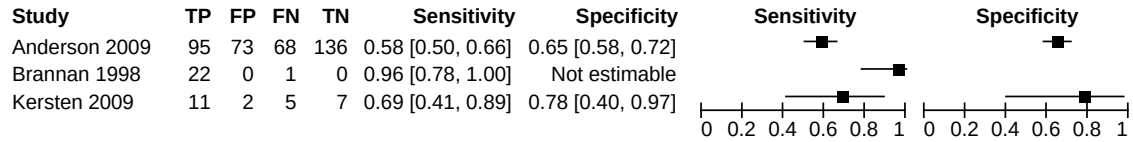


Table 21. Description of studies in the diagnostic test accuracy review: Mannitol vs. ECT

Author Year	Study design; Order of tests Study days; Challenges per day [N]; Time between challenges Concomitant treatment for asthma	REFERENCE STANDARD (ECT) Type; Duration (minutes) Load; Environmental conditions Follow-up time points Author definition of EIB/EIA	INDEX TEST (Mannitol) Type; Description Follow-up time points Author definition of EIB/EIA
Anderson[23] 2009	Cross sectional (prospective); ECT first 5 visits; 1; ECT – MCH: 1-2 d; ECT – mannitol: 1-2 d; MCH – mannitol: 1 day Asthma medications withheld according to guidelines	Treadmill; 6 80-90% max HR; RH dry (compressed) air; 20-25^{o}C 0, 5, 10, 15, 30 min post ECT ≥10% fall FEV_1	Dose: 0, 5, 10, 20, 40, 80, 160, 160, 160 mg; Process: exhale completely, take deep breath, hold for 5 sec, exhale through mouth, remove nose clip, repeat for each dose Measured 60 sec after each dose ≥15% fall FEV_1 or a ≥10% fall FEV_1 between consecutive doses
Brannan[47] 1998	Cross sectional (prospective); ECT or EVH first except for 3 participants 1 screening, 2-3 test d; 1; all completed in 35 d period NR	Bicycle ergometer; 8 90-100% max HR; NR 3, 5, 7, 10, 15, 30 min post ECT ≥10% fall FEV_1	Dose: 0, 5, 10, 20, 40, 80, 160,160, 160 mg; dry power inhalation; test stopped if ≥15% fall FEV_1 or cumulative dose of 635 mg administered FEV_1 measured at 60 sec after each dose and at 5, 10, 20, 30 min ≥15% fall FEV_1
Kersten[52] 2009	Cross sectional (prospective); ECT first 2 visits; 1; within 4 wk Asthma medication withheld according to guidelines	Treadmill; 6 90% max HR; RH dry air in a skating rink; 1^{o}C, 1, 3, 6, 9, 12, 15, 20 min post ECT ≥15% fall FEV_1	Dose: 0, 5, 10, 20, 40, 80, 160, 160, 160 mg; dry powder inhalation; Process: with nose clip; inhaled through mouth from near functional residual capacity to near total lung capacity, held for 5 sec, exhaled through mouth, removed nose clip, repeat for each dose Measured 60 sec after each dose; lowest dose causing cough noted ≥15% fall FEV_1 or ended when cumulative dose of 635mg mannitol reached

C = Celsius; d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; EVH = eucapnic voluntary hyperpnea; FEV_1 = forced expiratory volume in 1 second; HR = heart rate; max = maximum; MCH = methacholine; mg/ml = milligram per milliliter; MVV = maximal voluntary ventilation; NR = not reported; sec = second(s)

Table 22. Description of participants in the diagnostic test accuracy review: Mannitol vs. ECT

Author Year	Participants enrolled (N); analyzed (N) Age (mean±SD) Males: N (%)	Recruitment Country Index of activity (fitness level)	History of asthma N (%); Asthma severity; Atopic status N (%); History of ICS History of EIB/EIA	Baseline lung function (FEV_1) Baseline FEV_1 (% predicted)
Anderson[23] 2009	510; 375 (performed all tests) 24.3±10.2, range 6-50 182 (48.2)	Participants referred to clinic for investigation of asthma-type symptoms U.S. NR	0 (0); all had symptoms suggestive of asthma but no confirmed Dx; NAEPPII score 1.2±0.5 293 (78) NR NR	3.32±0.82 L 93.6±10%
Brannan[47] 1998	36; 23 24.5±6.4, range 18-40 16/36 (44.4)	Volunteers recruited through advertisement in local community Australia NR	36 (100); stable; 36 (100) atopic; 16 (44.4) 36 (100) self-report	NR 83.3±13.3% (range 66 to 120.3%)
Kersten[52] 2009	33; 25 12.4±2.0 17/25 (68.0)	Volunteers from outpatient clinic The Netherlands NR	25 (100); clinically stable; 25 (100) allergic asthma; 15 (60) ICS; 25 (100)	NR 97.4±16.6 % (range 65-132%)

EIB/EIA = exercise-induced bronchoconstriction/asthma; Dx = diagnosis; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; L = liters; NAEPPII = National Asthma Education and Prevention Program; NR = not reported; SD = standard deviation

Table 23. Methodological quality of studies in the diagnostic test accuracy review: Mannitol vs. ECT

Author Year	Representative spectrum	Selection criteria defined	Acceptable reference standard	Timing bias avoided	Partial verification avoided	Differential verification avoided	Clear reporting of index test	Clear reporting of reference standard	Index test blinded	Reference standard blinded	Uninterpretable index test results reported	Withdrawals explained
Anderson[23] 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Brannan[47] 1998	No	Yes	Yes	Yes	Yes	Yes	Yes	U	U	U	Yes	Yes
Kersten[52] 2009	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	U	U	Yes

U = unclear

Therapy Review

Literature Search

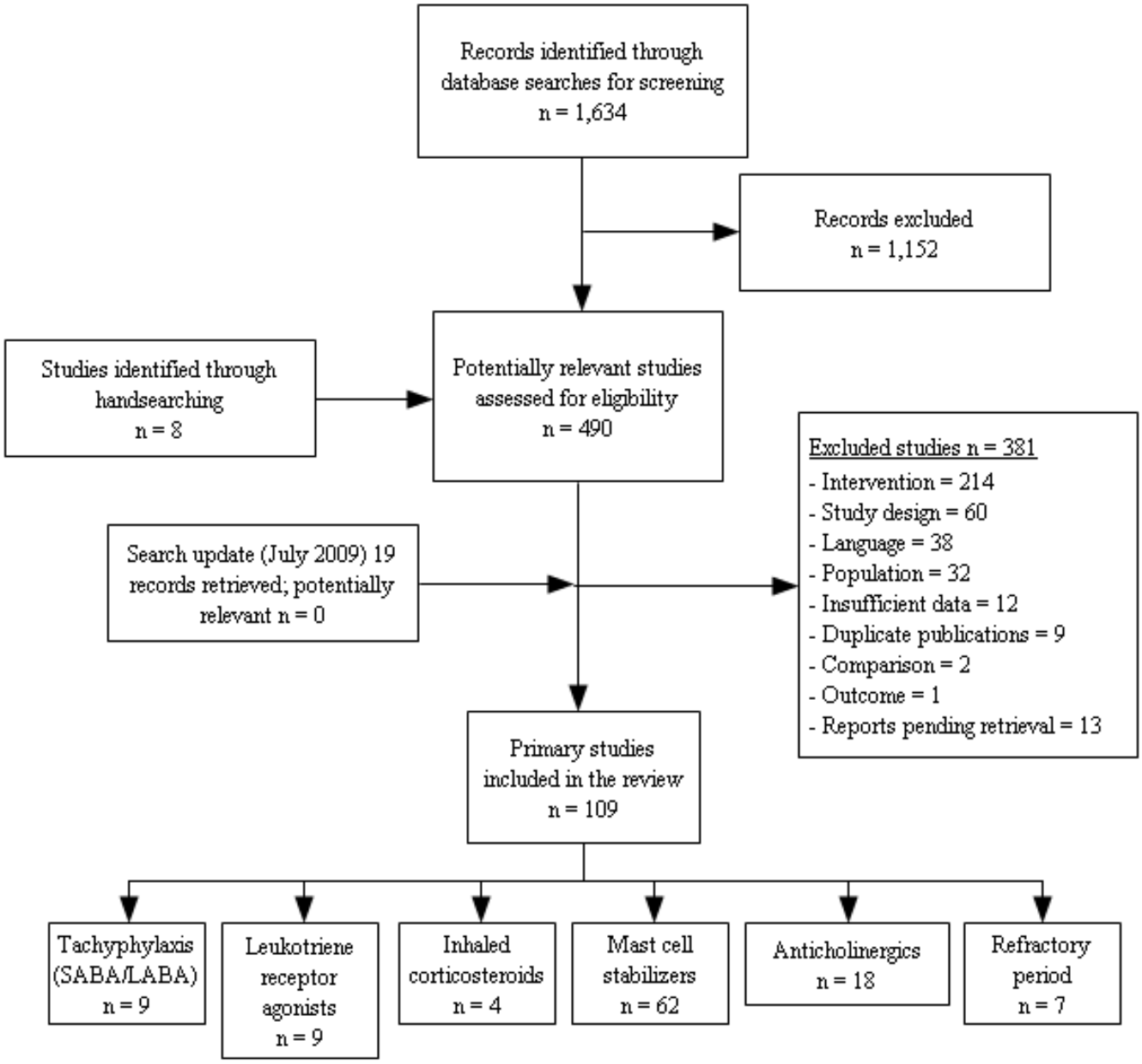
The search for controlled trials of the interventions targeted in this report identified 1,634 citations from electronic databases and eight by handsearching (Figure 13). Through screening of titles and abstracts, 490 references were selected for further examination. The full manuscripts of 13 citations could not be retrieved (Appendix D). Most of these were abstracts only available in supplementary conference proceedings. They were requested through interlibrary loan but did not arrive by the time this report was written. The search update identified an additional 19 citations; none met the screening criteria. We retrieved and evaluated the full-text of 477 potentially relevant articles. The application of the selection criteria resulted in 109 RCTs and CCTs being included; 368 studies were excluded.

During preliminary searches of the literature on mast cell stabilizing agents (MCS) three systematic reviews were identified. All three were published in the Cochrane Library[76-78] and two were also published in journal format.[104,161] Our search strategy included terms to identify new or additional trials that would update the existing reviews but none were identified. In consultation with AHRQ and the TEP, we made the decision to present a summary of these existing reviews (Appendix E).

The included articles addressed the following research questions: tachyphylaxis (n=9),[53-55,57-60,62,63] leukotriene receptor agonists (n=9),[44,64-71] inhaled corticosteroids (n=4),[72-75] MCS (n=62),[76-78,104,161]anticholinergics (n=18),[79-96] and a refractory period (warmup/cooldown; n=7).[97-103]

The main reasons for excluding studies were (1) the intervention did not address one of the research questions (n=214), (2) the study was not an RCT or CCT (n=60), (3) the study was not published in English (n=38), (4) the study population did not have a confirmed a diagnosis of EIB/EIA or included only children under the age of 6 (n=32). There were 24 studies excluded for other reasons. The list of excluded studies and reasons for exclusion are identified in Appendix D.

Figure 13. Therapy for EIB/EIA: Flow diagram for study retrieval and selection



Key Question T–1: Tachyphylaxis to Short-Acting Beta-Agonists or Long-Acting Beta-Agonists

Description of Included Studies

Nine RCTs met the inclusion criteria for the review on whether people with EIB/EIA develop tachyphylaxis to long-acting beta-agonists (LABA)[53-55,57-60] or to short-acting beta-agonists (SABA).[62,63] Tachyphylaxis is defined as a waning or a diminishing response to prophylactic doses of a beta-agonist to attenuate or prevent EIB/EIA when these agents are also used on a continuous basis. In the case of continuous SABA use, tachyphylaxis is also defined as a diminished ability to cause bronchodilation when needed to reverse bronchoconstriction. Six trials used a crossover design[55,57-59,62,63] and three were parallel trials.[53,54,60] The LABA agents studied were formoterol,[54] and salmeterol.[53,55,57-60] The duration of LABA use was every other day for 3 weeks,[58] daily use for 4 weeks,[54,55,57,59] or daily use for 8 weeks.[53,60]

The studies were published in peer reviewed journals between 1994 and 2009. Five were conducted in North America,[53,55,59,62,63] three in Europe,[54,57,58] and one in 12 different countries.[60] EIA was defined using different cutpoints of the maximum FEV_1 fall index: 15 percent or greater,[54,55,62,63] 18 percent or greater,[60] and 20 percent or greater.[57] The exercise challenge test (ECT) was performed on a treadmill[53,57,59,60] or bicycle ergometer.[54,55,62,63] The characteristics of the trials are summarized in Tables 24a and 24b.

The baseline characteristics of the participants are presented in Tables 25a and 25b. The number of patients enrolled ranged from 9 to 248. Two studies[58,59] included children only, two[62,63] included adults only, and five[53-55,57,60] included both adults and children. All participants had confirmed asthma; for most, their asthma was mild and stable.

Methodological Quality of Included Studies

Table 26 summarizes the methodological quality of included studies. Overall the quality of individual trials was high with a median Jadad score of 4 (IQR: 3, 4). Concealment of allocation was unclear in six trials[54,55,57-60] and adequately reported in one.[53] Two trials did not report their source of funding,[57,58] three had industry support,[53,59,60] three had government support,[54,62,63] and one had a combination of institution, government and private industry support.[55]

Quantitative Results: SABA

Two crossover trials that involved 1 week of regular (four times daily) SABA or placebo use prior to ECTs looked for evidence of tachyphylaxis to SABA.[62,63] The SABA agent studied was albuterol (salbutamol). Both studies compared baseline FEV_1 at the end of 1 week of use. Inman and O'Byrne[63] assessed the prophylactic effect on EIA of an additional prophylactic dose of SABA. Hancox et al.[62] did not address prophylaxis; however, did assess the bronchodilator effect of SABA following the ECT. Methodological differences precluded combining the data and the two studies are described separately.

Inman and O'Byrne[63] randomized 10 adults with asthma and EIA (maximum percent fall FEV_1 on pre-study ECTs ranged 15 to 45 percent) to 1 week of SABA 200µg or placebo four times per day. The washout period ranged from 7 to 21 days. Additional SABA use was allowed as needed throughout study weeks and the washout period. Baseline SABA use was less than 200µg per day and no other asthma medications had been taken in the previous month. No ECT was performed on day one of treatment and no baseline lung function measures were reported.

On day 8 of each treatment week, participants performed an ECT following a dose of placebo; on day 9, all performed an ECT following 200µg SABA (participants only were blinded to the prophylactic treatment taken).

Baseline FEV_1 after 1 week of treatment. The mean (±SE) pre-challenge FEV_1 on day 8 of the placebo week was 3.58±0.18L compared with 3.36±0.19L on day 8 of the SABA week; the pre-challenge FEV_1 on day 9 of the placebo week was 3.58±0.17L compared with 3.34±0.20L after the SABA week. The mean difference of 230 ml between treatment weeks was statistically significant (p=0.02).

Post bronchodilator FEV_1. On day 9, all participants received pre-challenge SABA 200µg. There was no significant difference between the placebo and SABA groups on the post-SABA FEV_1 prior to the ECT (3.94 ±0.18L versus 3.83 ±0.18L; p=0.06). No comparison on the degree of bronchodilation that occurred was reported.

Effect on EIA. On day 8 after pre-treatment with placebo, both groups experienced EIA following the ECT. The mean maximum percent fall in FEV_1 after the placebo week was 24.9±4.36 percent compared with a slightly greater fall of 29.4±4.71 percent after the SABA week. The difference of 4.5 percent was not statistically significant (p=0.12).

On day 9 following pre-challenge SABA, both groups experienced total protection from EIA. The mean maximum percent fall in FEV_1 in the placebo group was 1.1±0.76 percent compared with a slightly greater fall of 5.1±2.03 percent in the SABA group. The difference of 4 percent was statistically significant (p=0.05). The post-exercise FEV_1 measures were significantly lower at all time points over the recovery period after 1 week of continuous SABA use on both the day 8 placebo challenge (p=0.02) and the day 9 SABA challenge (p=0.01).

Other outcomes. Self-reported use of additional SABA for rescue during the placebo week was lower than during the SABA week (p>0.05).

The authors concluded that 1 week of regular SABA use resulted in a decrease in baseline FEV_1, a decreased prophylactic effect on EIA, and more pronounced EIA.

Hancox et al.[62] randomized eight, stable asthmatic women with EIA (maximum percent fall FEV_1 of 15 percent or more) to 6 to 10 days of SABA 200µg or placebo four times per day. There was no washout period. Baseline SABA use was not reported. All bronchodilating drugs were withheld for 8 to 36 hours pre-ECT and no prophylactic treatment was given prior to the ECT at the end of the treatment week. SABA 100 µg, 100 µg, and 200 µg were given at 5, 10, and 15 minutes post-ECT following FEV_1 measurements.

Baseline FEV_1 after 1 week of treatment. There was no significant difference between the mean pre-challenge FEV_1 after the SABA week compared with the placebo week (2.76L versus 2.80L).

Effect on EIA with no pre-treatment. At 5 minutes post-ECT the fall in FEV_1 was greater in the SABA arm and the group as a whole experienced EIA. The mean minimum absolute FEV_1 post-ECT after the SABA week was 2.28L (95 percent CI: 2.21, 2.35) compared with 2.55L (95 percent CI: 2.48, 2.62) after the placebo week (p=0.001). The percent fall in FEV_1 was not reported and could not be calculated. The authors reported that the magnitude of the bronchodilator response to SABA in both arms was similar (no data); however, the FEV_1 remained significantly lower in the SABA arm over the 25 minute recovery period despite administration of SABA at 5, 10, and 15 minutes.

The authors concluded that 1 week of regular SABA use results in more pronounced EIA and a suboptimal response to rescue medication.

Conclusions. The results from these two studies are equivocal on whether regular SABA use affects the baseline FEV_1 over time. The studies are consistent in presenting data that indicates that regular SABA use may lead to a greater degree of EIA. It is important to note that pre-treatment with SABA still offered complete protection to both groups in the one study.[63] There is some evidence to indicate tachyphylaxis develops to the bronchodilating effect of SABA as rescue medication.[62] The body of evidence is classified as "low."

Quantitative Results: LABA

Five studies compared regular LABA use to placebo,[54,55,58,59] four to salmeterol,[55,57-59] and one to formoterol.[54] Four studies reported regular LABA use for 4 weeks,[54,55,57,59] and one[58] used LABA treatment every other day for 21 days. Four studies were crossover trials[55,57-59] and one used a parallel group design.[54]

Formoterol versus placebo. Garcia et al.[54] randomized 19 stable asthmatics with EIA (maximum percent fall FEV_1 of 15 percent or more) to 28 days of formoterol 12µg twice daily (n=10) or to a matching placebo (n=9) in a parallel group design. In the month prior to the study, SABA use was less than two doses per week and other asthma treatment remained unchanged. The primary outcome was the change in the bronchoprotection index (BI) defined as the reduction in the maximum percent fall in FEV_1 after formoterol compared with no pre-treatment on the three test days.

On days 1, 14 and 28, participants refrained from taking all asthma medications and study drugs for 12 hours and performed two bicycle ECTs, 3 hours apart. The first took place with no prophylactic treatment; the second 30 minutes after taking formoterol.

Bronchoprotection index. The BI on day 1 was similar in the formoterol and placebo groups (71.3±32.6 percent versus 69.3±30.1 percent). During the study there was a significant decrease in the degree of protection offered by formoterol as the BI dropped to 52.3±31.7 percent on day 14 (p=0.012) and then to (27.8±32.6 percent) on day 28 (p=0.06). In the placebo group, the BI increased to 88.6±19.5 percent and 84.8±21.2 percent over the test days. The authors reported that these differences were not significant.

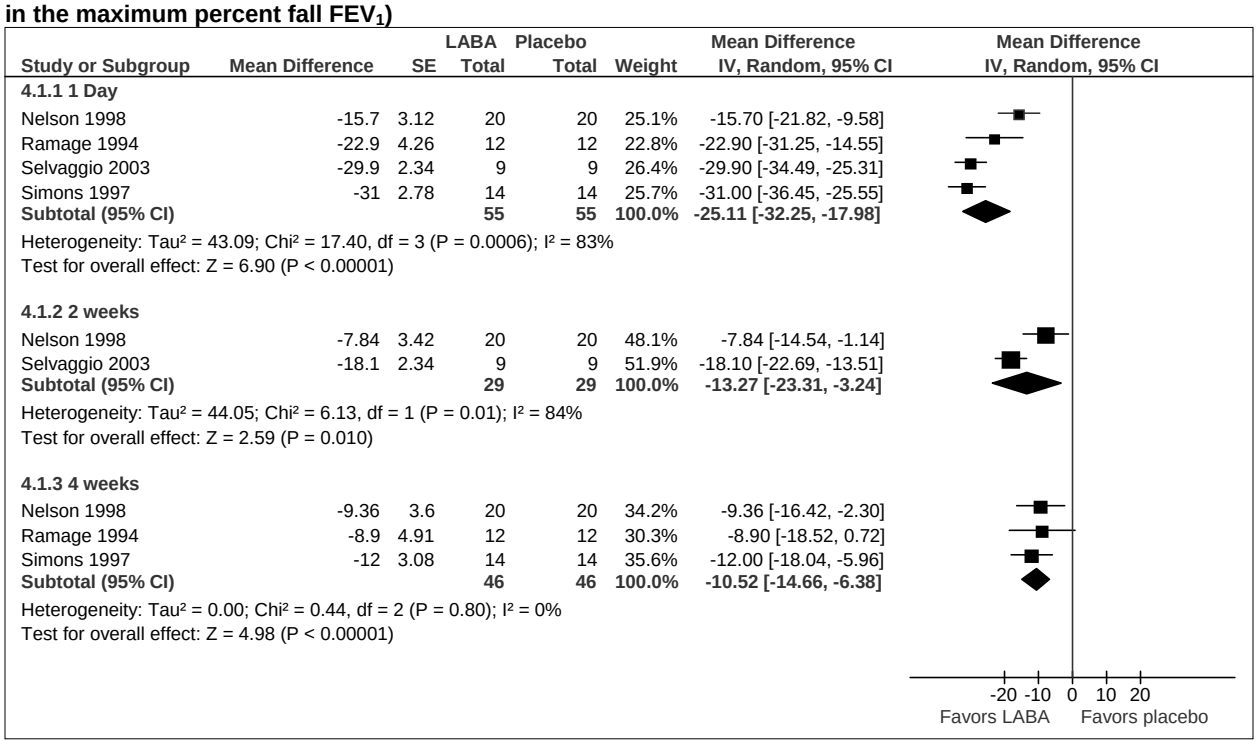
Complete protection (maximum percent fall FEV_1 less than 10 percent). On study days 1, 14 and 28, a prophylactic dose of formoterol conferred complete protection to 9 of 10, 5 of 8, and 5 of 10 patients in the formoterol group, respectively (p=0.28). On days 1 and 14, a prophylactic dose of formoterol conferred complete protection to 8 of 9 patients, and on day 28 to 7 of 9 patients in the placebo group.

The authors concluded that twice daily formoterol over 4 weeks caused a significant reduction in bronchoprotection against EIA. Tachyphylaxis was evident by day 14 but did not progress. A single pre-exercise LABA dose in non-regular users (i.e., placebo group) maintained its efficacy.

Salmeterol versus placebo. Four crossover studies[55,57-59] randomized groups to 3 or 4 weeks of salmeterol (50µg twice a day,[55,57] once a day,[59] or every other day for 3 weeks[58]) or to a matching placebo. Throughout the studies, the ECT was performed at 30 minutes,[55] 1 hour,[59] 6 hours,[57] and 9 hours[58] following administration of a study drug. The average fall in FEV_1 after the first ECT on day 1 in the four studies was 3.7 percent (range 5.0 to 11.9) in the LABA arms compared with 26.9 percent (range 20.5 to 36.6) in the placebo arms. The pooled difference favored the salmeterol (MD = 25.1 percent [95 percent CI: 32.3, 18.0) (Figure 14). The pooled results are presented as the MD between salmeterol and placebo at day 1, week 2 or 3, and week 4. The decreasing MD between salmeterol and placebo from day 1 to week 4 reflects the

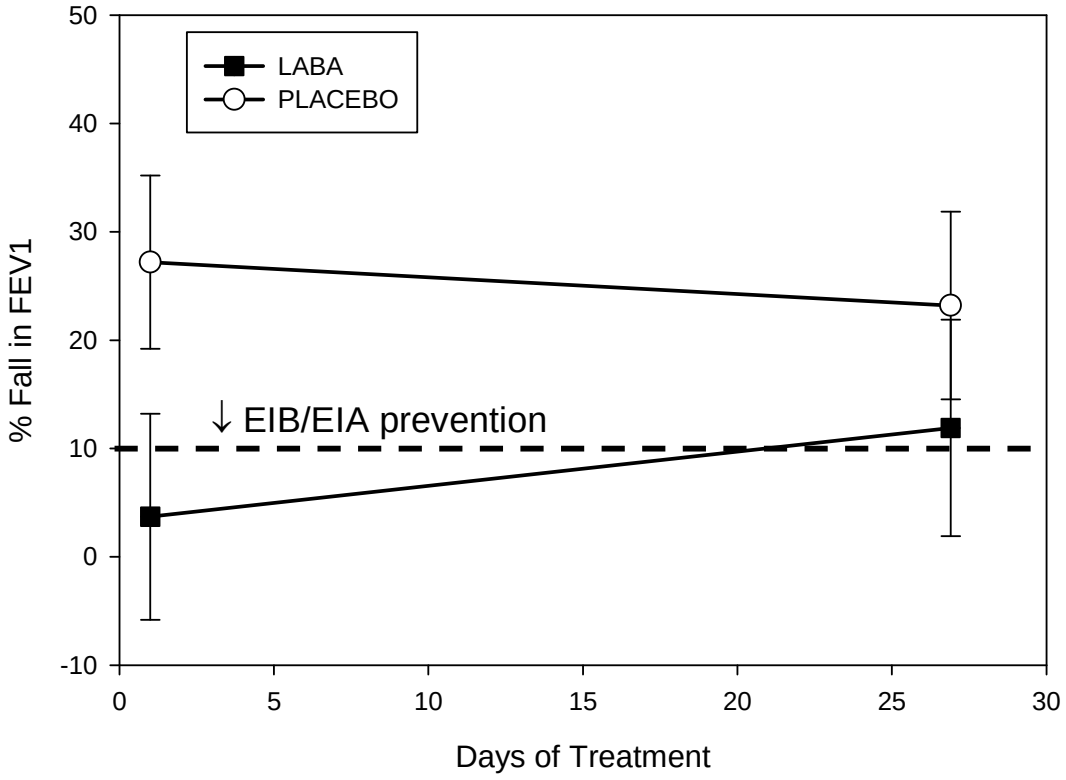
decreasing effect of the LABA as a prophylactic EIA agent; over the same time period the placebo effect remained constant.

Figure 14. Effectiveness of LABA vs. placebo: Change from day 1 to week 3–4 weeks after the first ECT (MD in the maximum percent fall FEV_1)



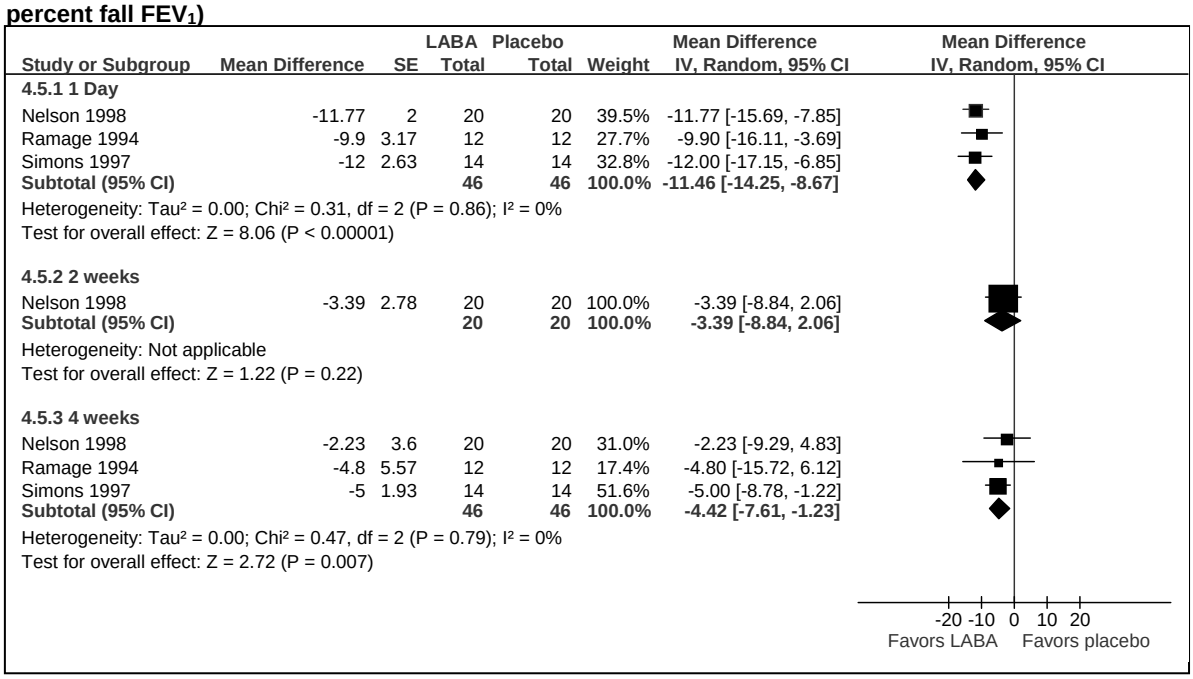
Maximum percent fall in FEV_1. The mean maximum fall in FEV_1 following an ECT after 2 and 4 weeks of continuous salmeterol use plus a pre-exercise dose was greater at week 4 than at day 1 (Figure 15). In contrast, the placebo arms showed a small decrease in the degree of EIA over the same time period. At the 4 week ECT, 30 minutes post-study drug, the average fall in FEV_1 was 11.4 percent (range 4.0 to 24.0) in the LABA arms compared with 21.3 percent (range 16.0 to 32.9) in the placebo arms; however, the pooled difference still favored the LABA (MD = 10.5 percent; 95 percent CI: 14.7, 6.4) (Figure 14). The timing of the ECT following administration of the study drug (30 minutes to 9 hours) was not a factor. Onset of the bronchodilator effect of salmeterol occurs in 10 to 20 minutes and lasts for at least 12 hours.[162]

Figure 15. Effects over time of LABA and placebo on the maximum percent fall in FEV_1 for the first ECT



Duration of action (maximum percent fall in FEV_1). Three studies[55,57,59] investigated the duration of action of salmeterol. Participants underwent a second ECT on the same day; the ECT was given 9 to 12 hours after administration of the study drug. The pooled results (Figure 16) show that salmeterol continued to have a greater protective effect than placebo at 4 weeks (MD = 4.4 percent; 95 percent CI: 7.6, 1.2). However, the protective effect had decreased from day 1 when the absolute MD was 11.5 percent (95 percent CI: 14.3, 8.7).

Figure 16. Effectiveness of LABA vs. placebo: Change from day 1 after the second ECT (MD in the maximum percent fall FEV_1)



Conclusions. Three to 4 weeks of regular LABA use results in a decreased prophylactic effect on EIA and more pronounced EIA. In studies that included a second ECT given 9 to 12 hours after the first ECT, the duration of the beneficial effects of LABA waned. The body of evidence is classified as "moderate."

LABA compared to other agents. Two studies compared regular use of salmeterol 50µg, two puffs twice daily versus a leukotriene receptor antagonist (LTRA) (montelukast 10mg) once in the evening for 8 weeks. The studies included 360 participants with stable asthma and confirmed EIA.[53,60] Both studies were funded by industry partners. The ECTs were performed near the end of the dosing interval for each drug (Table 24A). The pooled baseline fall in FEV_1 in both groups in both studies (34.9 percent for LABA and 33.9 percent for LTRA) indicated that the participants experienced moderate to severe EIA. Both agents attenuated the EIA response after 3 days of treatment to a similar degree. The mean fall in the LABA group was reduced to 19.8 percent compared with 18.2 percent in the LTRA group; this difference was not significant (MD = 1.0 percent; 95 percent CI: -2.2, 4.2) (Figure 17). Both agents continued to be effective; however, montelukast maintained the same level of effectiveness at 4 and 8 weeks compared with a slight decrease in effect with regular use of salmeterol. At 8 weeks, the mean fall in the LABA group was 23.0 percent compared with 17.1 percent in the LTRA group; this difference was significant (MD = 5.4 percent; 95 percent CI: 2.2, 8.7). The studies also reported that a combined 52 percent of LABA participants compared with 65 percent of LTRA participants experienced falls in FEV_1 of less than 20 percent at 8 weeks.

Although indirect evidence, these results lend support to other results that indicate some degree of tachyphylaxis develops early on with regular daily use of LABA. Furthermore, regular daily use of LABA lessens its ability to attenuate EIA when prophylactic doses are taken before exercise.

Figure 17. Effectiveness of LABA vs. LTRA: Change from day 1 to week 8 (MD in the maximum percent fall FEV_1)

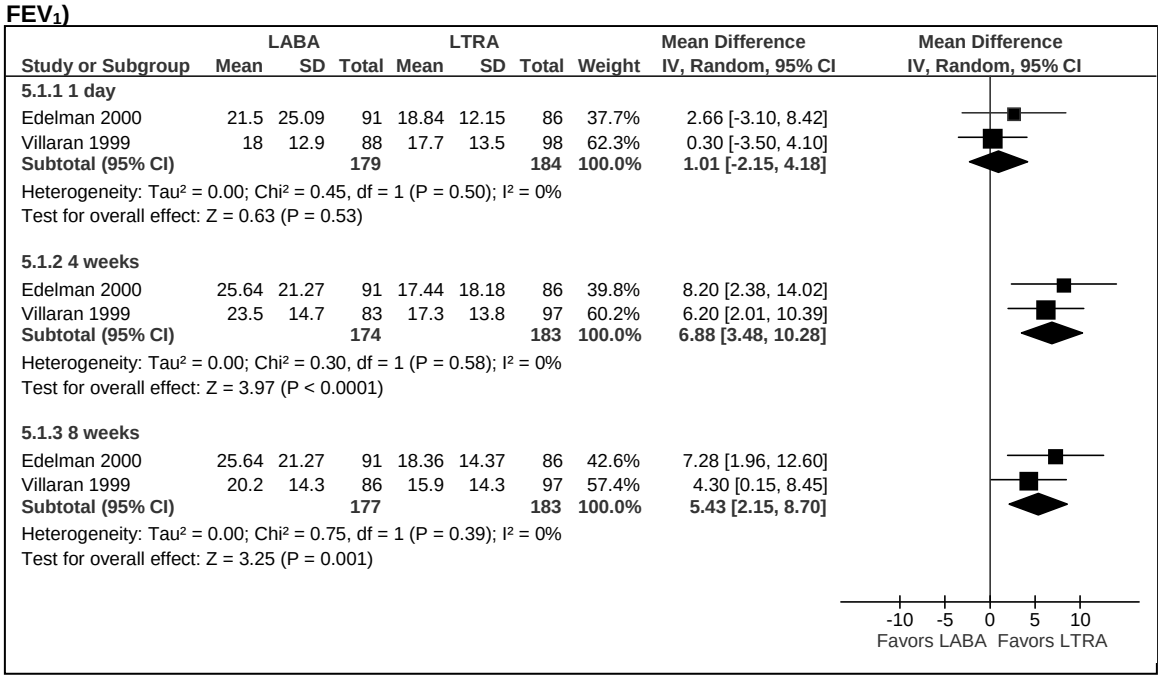


Table 24a. Description of trials in the therapy review: Tachyphylaxis to LABA

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Treatment Groups: drug; dose; delivery device; time pre-ECT	ECT: type; duration; predicted HR; temp; RH; % Study days; challenges/day [N]; time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Formoterol vs. placebo					
Garcia[54] 2001 Spain Clinic	Journal article Fondo de Investigación Sanitaria Parallel	F: 10; P: 9 F: 10; P: 9 0	F: 12 µg/bid x 28 d; MDI; no pre-Tx and 30 min P: 2 puffs bid x 28 d; MDI; 30 min	Bicycle ergometer; 6 min; 85% 21.2°C; 48.30% RH 4 [1 screen then days 1, 14, 28] 2; 3 hr SABA, NCS, SCG, calcium antagonists, antihistamines, ipratropium bromide and study medication x 12 hr	≥15% Primary: max % fall FEV_1; change bronchoprotection index Secondary: complete protection; clinical protection FEV_1 measured at 1, 3, 5, 8, 10, 15, 20, 30, 40, 60 min post ECT NR
Salmeterol vs. placebo					
Nelson[55] 1998 U.S. Clinic	Journal article National Heart, Lung, and Blood Institute; NIH; Glaxo Wellcome Corp. Crossover	20 20 0	Salm: 50 µg bid x 30 d; MDI; 30 and 9.5 hr P: 2 puffs bid x 30 d; MDI; 30 min and 9.5 hr	Bicycle ergometer; 4 min; 740±246 kilopond meters/min cold air (-8.5±1.3°C); NR 7 [1 screen then 1, 14 and 29 d of each study mo] 2; 9 hr ICS, methylxanthines, SABA, NS x 12 hr; methylxanthines x 24 hr	≥15% Primary: mean % fall FEV_1 10 min post-ECT; duration of action Secondary: FEV_1 L; complete protection FEV_1 measured at 10 min post ECT NR
Ramage[57] 1994 United Kingdom Clinic	Journal article NR Crossover	12 12 0	Salm: 50 µg bid x 4 wk; MDI; 6 and 12 hr P: 1 puff bid x 4 wk; MDI; 6 and 12 hr	Treadmill; 6 min; 85% dry air; NR 5 [1 screen, and first and last day of each Tx period] 2; 6 hr SABA, SCG, methylxanthines x 8 hr; 24 hr and 24 hr	≥20% Primary: max % fall FEV_1; difference between 1 and 4 wk dosing Secondary: Pre-exercise FEV_1 L; complete protection; clinical protection FEV_1 measured at 5, 10, 20, 30, 60 min post ECT NR

Ach = anticholinergic; AE = adverse events; AUC = area under curve; bid = twice/day; C = Celsius; d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; F=formoterol; FEV_1 = forced expiratory volume in 1 second; hr = hour(s); HR = heart rate; ICS = inhaled corticosteroid; L = liter; LABA = long-acting beta-agonist; LTRA = leukotriene receptor antagonist; µg = microgram; max = maximum; m = meters; M=montelukast; MDI = metered dose inhaler; min = minute(s); mg = milligram; mo = month(s); NR = not reported; NS=nedocromil sodium; P = placebo; PEF = peak expiratory flow; RH = relative humidity; SABA = short-acting beta-agonist; SALM=salmeterol; SCG = sodium cromoglycate; temp = temperature; Tx = treatment; URTI = upper respiratory tract infection; wk = week(s)

Table 24a. Description of trials in the therapy review: Tachyphylaxis to LABA (continued)

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Treatment Groups: drug; dose; delivery device; time pre-ECT	ECT: type; duration; % predicted HR temp; RH; Study days; challenges/day [N]; time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Salmeterol vs. placebo					
Selvaggio[58] 2003 Italy NR	Abstract NR Crossover	9 9 0	Salm: 50 µg every other d x 21 d; diskus; 9 hr P: 1 puff every other d x 21 d; diskus; 9 hr	NR 4 [day 1 and 21 of each Tx period]; 1 20 d NR	NR Primary: max % fall FEV_1 Secondary: bronchoprotective effect NR
Simons[59] 1997 Canada Clinic	Journal article Glaxo Wellcome Inc. Crossover	16 14 2	Salm: 50 µg/d x 28 d; MDI with nebulizer; chronolog; 1 and 9 hr P: 2 puffs/d x 28 d; MDI with nebulizer chronolog; 1 and 9 hr	Treadmill; 8 min; 90% 21.7-22.4°C; 46.5-53.9% RH 4; 2 8 hr SABA, pseudoephedrine x 8 hr	NR Primary: max % fall FEV_1; duration of action Secondary: PEF L/min P: exacerbation=1, chest tightness=1. Salm: headache=3
Salmeterol vs. montelukast					
Edelman[53] 2000 U.S. [17 sites] Clinic	Journal article Merck Parallel	Salm: 94; M: 97 Salm: 86; M: 91 Salm: 8; M: 6	Salm: 50 µg/bid x 8 wk; MDI; 9 hr M:10 mg/d x 8 wk; tablet; 21 hr	Treadmill; 6 min; 80-90% room temp; dry air 3; 1 day 1-3, wk 4, wk 8 SABA x 6 hr	≥20% Primary: max % fall FEV_1 Secondary: change in max % fall; FEV_1 L; complete protection FEV_1 measured at 0, 5, 10, 15, 30, 45, 60 min post ECT Salm vs. M: asthma 7% vs. 3%; headache 6% vs. 5%; URTI 10% vs. 14%; total AE Salm vs. M: 40% vs. 41%
Villaran[60] 1999 25 centers in 12 countries Clinic	Journal article Merck Parallel	R=Salm: 95; M: 102; A=Salm: 88; M: 100 W=Salm: 7; M: 2	Salm: 50 µg bid x 8 wk; MDI; 8-12 hr M: 10 mg OD; tablet; 20-24 hr	Treadmill; 8 min; 80-90% room temp; compressed dry air 5 [2 screen, 3rd d, wk 4 and 8]; 1 in evening 25-28 d SABA; antihistamines x 8 hr; 48 hr; all others 1-2 wk	≥18% Primary: max % fall FEV_1 at 8wk; AUC Secondary: change max % fall FEV_1; FEV_1 L change from baseline; % protection FEV_1 measured at 5, 10, 15, 30, 45, 60 min post ECT Salm vs. M: bronchoconstriction 32% vs. 24%; headache 8% vs. 10%; pharyngitis 7% vs. 8%; URTI 8% vs. 3%

Table 24b. Description of trials in the therapy review: Tachyphylaxis to SABA

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Treatment Groups: drug; dose; delivery device; time pre-ECT	ECT: type; duration; temp; RH; % predicted HR Study days; challenges/day [N]; time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Hancox[62] 2002 Canada Clinic	Journal article Father Sean O'Sullivan Research Centre; Ont Thoracic Society Crossover	9 8 1	Sal: 200 µg qid x 7 d; MDI; 8 hr P: 2 puffs qid x 7 d; MDI; 8 hr	Bicycle ergometer; incremental over 7 min; 80% NR; dry air 1; 1 NA LABA 36 hr; SABA 8 hr; IB 12 hr IB 20 µg/puff allowed for relief	≥15% Primary: change in bronchodilator response to Sal post-ECT Secondary: max % fall FEV_1; FEV_1 L; FEV_1 measured at 1, 3, 5, 10, 15, 20, 25, 30 min Exacerbation=1 (Tx period NR)
Inman[63] 1996 Canada Clinic	Journal article Ontario Thoracic Society Crossover	10 10 0	Alb: 200 µg qid x 7 d; MDI; immediate P: 2 puffs qid x 7 d; MDI; immediate	Bicycle ergometer; 5 min; 67.2±10.8% of max work rate 21.5°C; <10% RH 4; 1 24 hrs SABA x 8 hr; caffeine x 24 hr	≥15% Primary: max % fall FEV_1; Secondary: FEV_1 L FEV_1 measured at 5, 10, 15, 30 min NR

Alb=albuterol; d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; hr = hour(s); HR = heart rate; IB = ipratropium bromide; L = liter; LABA = long-acting beta-agonist; µg = microgram; max = maximum; MDI = metered dose inhaler; min = minute(s); NR = not reported; qid = four times a day; RH = relative humidity; P=placebo; SABA = short-acting beta-agonist; sal=salbuterol; temp = temperature; wk = week(s)

Table 25a. Baseline characteristics of patients in trials in the therapy review: Tachyphylaxis to LABA

Author Year	Age (mean±SD) Males: N (%)	Asthma status	Pulmonary function (% predicted FEV_1 / mean±SD)	Max % fall FEV_1 (mean±SD)	Smoking status: N (%)	Atopic status: N (%)	ICS history: N (%)
Formoterol vs. placebo							
Garcia[54] 2001	F: 22.8±6.1 P: 25.4±5.2 F: 3/10 (30) P: 5/9 (56)	Stable x 1 mo and throughout trial	F: 104.4±19.4 P: 97.7±13.4	Control ECT F: 21.5±10.0 P: 18.11±10.0	NR	NR	F: 3/10 (30) P: 3/9 (33.3)
Salmeterol vs. placebo							
Nelson[55] 1998	29±8.9 9/20 (45)	Stable but with mixed severity	93±13.4	Control ECT 24±8.9	Non-smokers	Mixed	6/20 (30)
Ramage[57] 1994	25.8±5.0 8/12 (66.7)	Stable mild	105.7±20.5	Placebo ECT 34.8±17.0	Non-smokers	7/12 (58.3)	3/12 (25)
Selvaggio[58] 2003	Range 6-16 NR	NR	NR	Placebo ECT 36.6±7.6	NR	NR	NR
Simons[59] 1997	13.1±1.3 7/16 (43.8)	Stable	93.4±12.7	Placebo ECT 24±12	NR	16/16 (100)	16/16 (100)
Salmeterol vs. montelukast							
Edelman[53] 2000	Salm: 26; range 15-46 M: 26.5, range 15-46 Salm: 54/94 (57) M: 46/97 (47)	Stable with range of severity	Salm: 88.0±13.5 M: 87.1±11.2	Control ECT Salm: 36.6±12.3 M: 37.0±11.5	Non-smokers ≥1yr	NR	None
Villaran[60] 1999	All: 27±5.4 Salm: 45/95 (47) M: 53/102 (52)	Stable mild	Salm: 87.2±14 M: 86.6±13.7	Control ECT Salm: 30.5±10.5 M: 33.3±12.1	Past: 170/197 (86) Never 27/197 (13.7)	NR	Salm: 6/95 (6.3) M: 14/102 (13.7)

ECT = exercise challenge test; F = formoterol; FEV_1 = forced expiratory volume in 1 second; M = montelukast; mo = month(s); NR = not reported; P = placebo; salm = salmeterol; SD = standard deviation

Table 25b. Baseline characteristics of patients in trials in the therapy review: Tachyphylaxis to SABA

Author Year	Age (mean±SD) Males: N (%)	Asthma status	Pulmonary function (% predicted FEV_1 / mean±SD)	Max % fall FEV_1 (mean±SD)	Smoking status: N (%)	Atopic status: N (%)	ICS history: N (%)
Hancox[62] 2002	26, range 18-44 1/9 (11.1)	Stable	FEV_1/FVC=83±10 % FEV_1 =2.8 L	Placebo ECT 10%	NR	NR	1/9 (11.1)
Inman[63] 1996	24.5, range 19-37 7/10 (70)	Stable	85.4±6.3	Control ECT 15-45%	Non-smokers	10/10 (100)	None

ECT = exercise challenge test; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; NR = not reported; SD = standard deviation

Table 26. Quality assessment of trials in the therapy review: Tachyphylaxis to LABA and SABA

Author Year	Described as randomized?	Described as double-blind?	Description of withdrawals/ dropouts?	Method of randomization described and appropriate?	Method of double-blinding described and appropriate?	Method of randomization described but inappropriate?	Method of double-blinding described but inappropriate?	Overall Score: Jadad	Concealment of allocation
Edelman[53] 2000	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Garcia[54] 2001	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Hancox[62] 2002	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Inman[63] 1996	Yes	Yes	Yes	No	No	No	No	3	Unclear
Nelson[55] 1998	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Ramage[57] 1994	Yes	Yes	Yes	No	No	No	No	3	Unclear
Selvaggio[58] 2003	Yes	Yes	Yes	No	No	No	No	3	Unclear
Simons[59] 1999	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
Villaran[60] 1999	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear

Key Question T–2: Leukotriene Receptor Antagonist Therapy

Description of Included Studies

Nine randomized crossover trials[44,64-71] met the inclusion criteria for the review comparing a single dose of leukotriene receptor antagonist (LTRA) with no treatment or placebo to prevent a 10 percent or greater drop in FEV_1 compared with no treatment or placebo. The studies were published between 1999 and 2007. Six trials were conducted in North America,[44,64,65,67,68,71] two in Europe,[66,69] and one[70] involved multiple sites in North and South America.

The drugs studied were montelukast,[44,64-66,68-71] zafirlukast,[65,67] and zileuton.[65] They were administered between 2 and 24 hours prior to an ECT. The thresholds for EIB/EIA measured by the FEV_1 fall index were 10 percent or greater,[44,66] 15 percent or greater,[64,65,69] and 20 percent or greater.[67,68,70,71] The ECT was performed on a treadmill,[64,66-71] or bicycle ergometer.[44,65] The characteristics of the trials are summarized in Table 27.

The baseline characteristics of the participants are presented in Table 28. The number of patients enrolled ranged from 10 to 62 (total 267). Three studies[64,67,69] included children only, four[65,66,68,70] included adults only, and two[44,71] included both children and adults. In eight trials[44,64-71] all participants had a confirmed diagnosis of asthma; in the remaining trial[44] 36 percent of the participants had confirmed asthma. Participants had stable asthma with lung function greater than 85 percent predicted.

Methodological Quality of Included Studies

Table 29 summarizes the methodological quality of the included studies. Overall, the quality of the nine trials was good; the median Jadad score was 3 (IQR: 3, 5). Concealment of allocation was unclear in eight trials,[44,64-69,71] and adequately reported in one.[70] Two trials[66,69] did not report their source of funding, five[44,67,68,70,71] reported pharmaceutical industry support, and two[64,65] had government/institutional support. The body of evidence is classified as "moderate."

Quantitative Results

Pulmonary function measures. All nine trials recorded the maximum percent fall in FEV_1 on an ECT performed 2 hours or less following drug administration. The times at which later ECTs were performed varied across studies thus data were categorized into two groups: 8 to 12 hours and 24 hours.

The mean fall in FEV_1 on the placebo challenges ranged from 15.0 to 23.2 percent (average 18.5) indicative of mild EIA. The average fall in FEV_1 in the LTRA arms after the first ECT ranged from 7.6 to 13.3 percent (average 10.9). The absolute MD = 8.3 percent (95 percent CI: 6.9, 11.0) and represents clinical protection of approximately 41 percent over placebo. Substantial heterogeneity (I^2=65 percent) was identified (Figure 18).

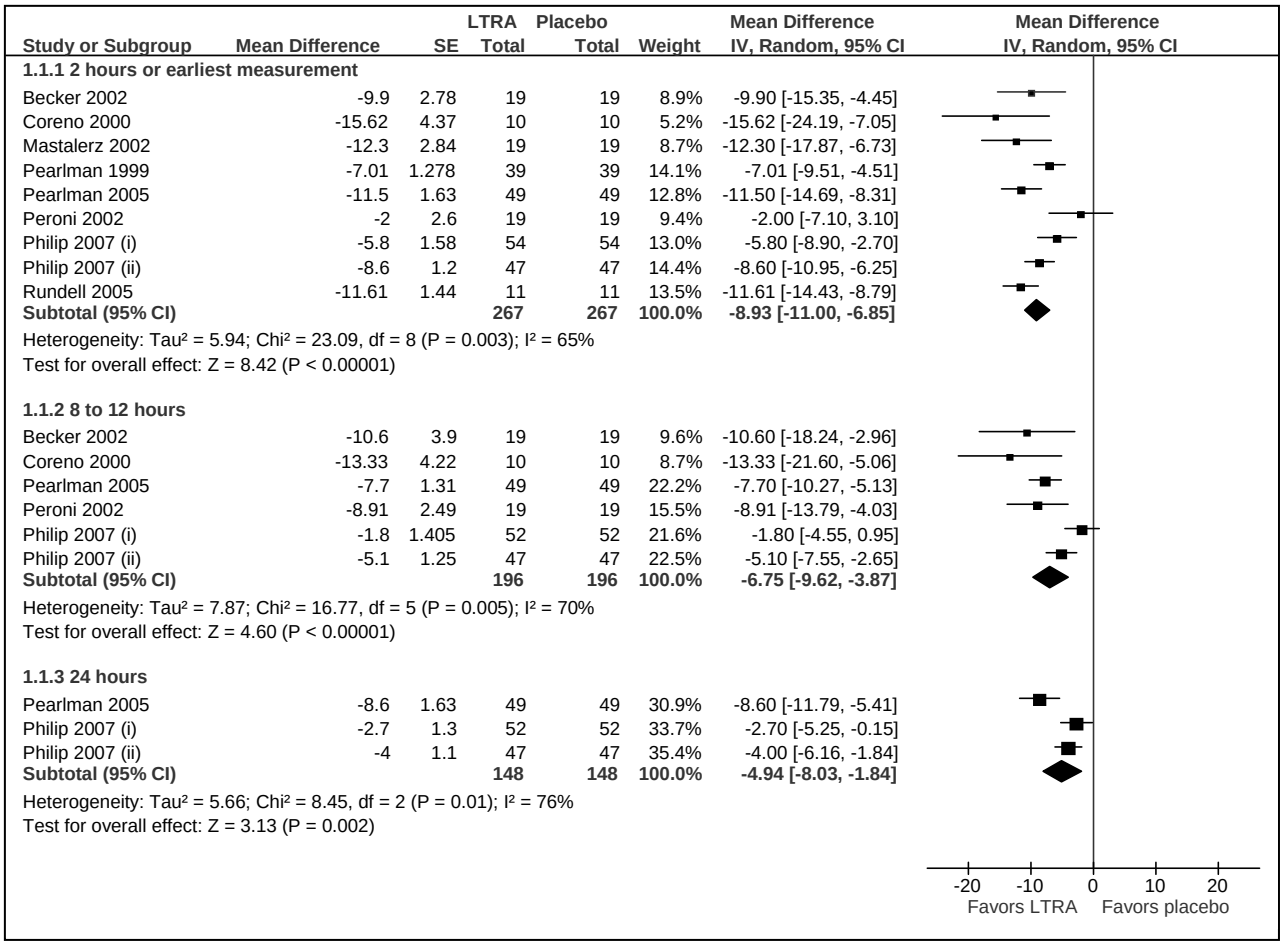
Six of the trials[64,65,68-71] recorded the mean maximum percent fall in FEV_1 on an ECT 8 to 12 hours after drug administration. The difference between groups ranged from 1.8 to 13.3 percent and all favored LTRA. The absolute MD = 6.8 percent (95 percent CI: 3.9, 9.6). Substantial heterogeneity (I^2=70 percent) was identified (Figure 18).

The difference in the mean fall in FEV_1 on an ECT 24 hours following drug administration was reported in three trials[68,70,71] and ranged from 4 to 8.6 percent in favor of LTRA. The average fall in the placebo arms was 13.8 percent (range 10.7 to 16.9) compared with 8.7 percent (range 8.3 to 10) in the LTRA arms. The pooled results indicate that LTRA remained significantly more

effective than placebo in attenuating EIA (MD = 4.9 percent; 95 percent CI: 8.0, 1.8). Substantial heterogeneity (I^2=76 percent) was identified (Figure 18).

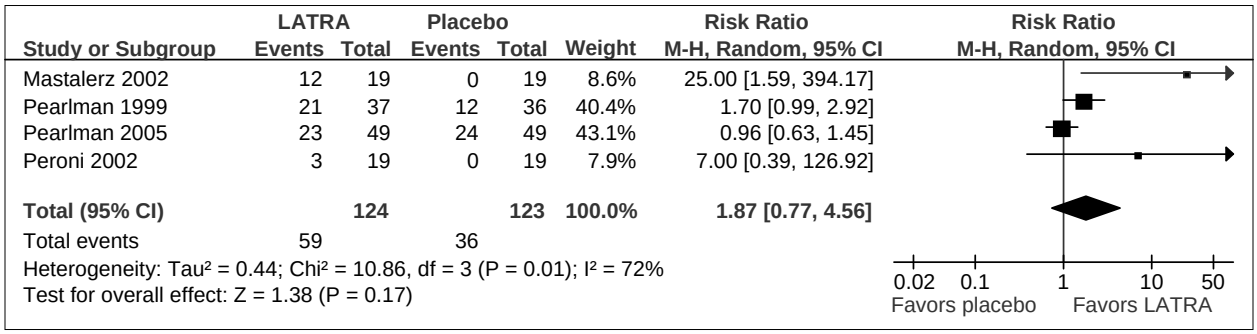
The source of the heterogeneity could not be explained by subgroup analyses based on age, dose of study medication, or funding source. Other subgroup analyses (e.g., ICS use, atopic status) could not be performed due to lack of data.

Figure 18. LTRA vs. placebo in pre-exercise treatment of EIB/EIA: Maximum decrease in FEV_1



Complete protection. Four trials[66-69] reported the proportion of participants who received complete protection as an outcome measure. Using less than a 10 percent fall in FEV_1 as the cutpoint, the pooled estimate indicated that there was no significant difference in the number who achieved complete protection with LTRA (RR = 1.9; 95 percent CI: 0.8 to 4.6) compared with placebo. Substantial heterogeneity (I^2=72 percent) was identified (Figure 19).

Figure 19. LTRA vs. placebo in pre-exercise treatment of EIB/EIA: Achievement of complete protection (maximum percent fall FEV_1 is less than 10 percent)



Adverse effects. One study[69] reported that there were no adverse effects using a 5 mg dose of montelukast. Using 10 mg of montelukast, three trials reported non-serious adverse effects that included mild headache,[68,70,71] nausea,[68] nervousness,[68] arthralgia,[71] and myalgia.[71] One study[67] reported dizziness, pharyngitis, fatigue and headache at a dose ranging from 5 to 40 mg of zafirlukast. The occurrence of side effects, however, was not markedly different between the treatment and placebo groups (Table 27).

Table 27. Description of trials in the therapy review: LTRA

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Treatment Groups: drug; dose; delivery device; time pre-ECT (min)	ECT: type; duration (min); % predicted HR temp; RH; Study days; challenges/day [N]; time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Becker[64] 2002 Canada Clinic	Abstract Industry/Institution Crossover	19 19 0	M: 5 mg; chewable tablet 1, 2, 4, 8 hr P: NA; chewable tablet 1, 2, 4, 8 hr	Treadmill; 8; 50% 20°C; NR 3; 4 1, 2, 4 hr NR	≥15% Primary: max % fall FEV_1 Secondary: none FEV_1 measured at 1, 2, 4, 8 hr post ECT NR
Coreno[65] 2000 U.S. Clinic	Journal article Government/iInstitute Crossover	10 10 0	M: 10 mg; oral 1, 4, 8, 12 hr Za: 20 mg; oral 1, 4, 8, 12 hr ZI: 600 mg; oral; 1, 4, 8, 12 hr P: NA; oral 1, 4, 8, 12 hr	Bicycle ergometer; 4; 790±7 kilopound m/min frigid air -5 to -16°C; NR 5 (1/wk); 4 4 hr ICS continued; BD x 24 hr; antihistamine x 72 hr	≥15% Primary: mean % fall FEV_1 Secondary: FEV_1 L; FEV_1 measured at 10 min post each of 4 ECTs NR
Mastalerz[66] 2002 Poland NR	Journal article NR Crossover	19 19 0	M: 10 mg; tablet 1 hr P: NA; tablet 1 hr	Treadmill; 6-8; 80-90% 20-25°C; ≤50% 3 d intervals; 1 3 d No; BD; NR	≥10% Primary: max % fall FEV_1 Secondary: Complete protection FEV_1 measured at 5, 10, 15, 20, 30 min post ECT NR
Pearlman[67] 1999 U.S. Clinic	Journal article Zeneca Pharmaceuticals 3 way crossover; 2 independent groups; 2 doses Za, 1 P	39 36 3	G1: Za:, 5 mg; 20 mg; oral, 4 hr G2: Za: 10 mg; 40 mg; oral 4 hr G1: P: NA; oral G2: P: NA; oral 4 hr	Treadmill; 6-8; 80-90% room temp; NR 4; 1 4-14 d ICS, SCG x 4wk; astemizole x 3 mo, LABA x 48 hr	≥20% Primary: max % fall FEV_1 Secondary: complete protection (at 20%) FEV_1 measured at 5, 10, 15, 30 min post ECT Za: dizziness=5, pharyngitis=3, fatigue=4, headache=2. P: dizziness=4, pharyngitis=3, fatigue=2, headache=3

AE = adverse events; BD = bronchodilator; d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; hr = hour(s); HR = heart rate; ICS = inhaled corticosteroid; L = liter; LABA = long-acting beta-agonist; M=montelukast; m = meter; max = maximum; med = medication; min = minute(s); mg = milligram; NA = not applicable; NR = not reported; P = placebo; RH = relative humidity; SABA = short-acting beta-agonist; temp = temperature; wk = week(s); za= zafirlukast; zi=zileuton

Table 27. Description of trials in the therapy review: LTRA (continued)

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Treatment Groups: drug; dose; delivery device; time pre-ECT	ECT: type; duration (min); % predicted HR temp; RH; Study days; challenges/day [N]; time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events (n)
Pearlman[68] 2005 U.S. Clinic (9 centers)	Journal article Merck Research Laboratories Crossover	51 49 2	M: 10 mg; oral 2, 12, 14 hr P: NA; oral 2, 12, 24 hr.	Treadmill; 6; 80-90% NR; NR 4 (3-7 d between ECTs) 3/24 hr; 10, 12 hr ICS allowed; SABA x 8 hr	≥20% Primary: max % fall FEV_1 (2 hr, 12 hr, 24 hr) Secondary: FEV_1 L (% change); % protection; complete protection (at 10, 15, 20%); clinical protection FEV_1 measured at 0, 5, 10, 15, 30, 45, 60 min post ECT No serious clinical/lab AE. M: nausea, nervousness=2; exacerbation=1, influenza=1 (these 2 withdrew)
Peroni[69] 2002 Italy Lived in Italian Alps at high altitude	Journal article NR Crossover	19 19 0	M: 5 mg; NR 2, 12 hr P: NA; NR 2, 12 hr	Treadmill; 6; 80% 21°C; 40-50% RH 4 (3-5 d apart); 2 10 hr Meds continued; BD x 12 hr	≥15% Primary: max % fall FEV_1 Secondary: % protection; clinical protection; FEV_1 L; FEV_1 measured at 1, 5, 10, 15, 20, 30 min; No AE were observed
Philip[70] 2007a U.S., South America (Peru) Clinic (5 centers)	Journal article Merck Research Laboratories Crossover	47 45 1	M: 10 mg; oral 2, 8.5 and 24 hr P: NA; oral 2, 8.5 and 24 hr	Treadmill; 6; 80-90% room temp; dry air 5 (3-7 d between ECTs); 3/24 hr 2, 8.5, 12 hr ICS allowed, all others excluded; SABA x 8 hr	≥20% Primary: max % fall FEV_1 (2 hr, 8.5 hr, 24 hr) Secondary: FEV_1 L (mean % max change); mean % fall FEV_1 FEV_1 measured at 0, 5, 10, 15, 30, 45, 60 min No serious AE; M: 6/47; P: 7/47 (2/7 were headaches)

Table 27. Description of trials in the therapy review: LTRA (continued)

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Treatment Groups: drug; dose; delivery device; time pre-ECT	ECT: type; duration (min); % predicted HR temp; RH; Study days; challenges/day [N]; time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events (n)
Philip[71] 2007b U.S. NR	Journal article Merck Research Laboratories Crossover	62 53 9	M: 10 mg; oral 2, 12, 24 hr P: NA; oral 2, 12, 24 hr	Treadmill; 6; 80-90% room temp; dry air 2; 3/24 hr 10, 12 hr Meds continued; BD x 8 hr	≥20% Primary: max % fall FEV_1 Secondary: complete protection (at 20%) FEV_1 measured at 0, 5, 10, 15, 30, 45, 60 min post ECT; AE=7 (none discontinued); M: arthralgia and myalgia=1; P: flushing and headache=1; P: diarrhea=1, headache=1, nausea=1
Rundell[44] 2005 U.S. College athletes (volunteers)	Journal article Merck Research Laboratories Crossover	11 11 0	M: 10 mg; oral 6-8 hr P: NA; oral 6-8 hr	Bicycle ergometer; 6; NR -3°C; 50% RH 4; 1 2-3 d None on asthma med	≥10% Primary: max % fall FEV_1 Secondary: FEV_1 L (% change); % protection; complete protection (at 10%); clinical protection FEV_1 measured at 5, 10, 15 min post ECT NR

Table 28. Baseline characteristics of patients in trials in the therapy review: LTRA

Author Year	Age (mean±SD) Males: N (%)	Asthma status	Pulmonary function % predicted FEV_1 (mean±SD)	Max % fall FEV_1 (mean±SD)	Smoking status: N (%)	Atopic status N (%)	ICS history: N (%)
Becker[64] 2002	11.0±2.7 NR	Stable	88.6±14.4	Control ECT 21.1±9.6	NR	NR	NR
Coreno[65] 2000	29±9.5 4/10 (40)	Stable	93±12.6	Placebo ECT 21±15.8 to 26±15.8	Non-smokers	NR	6/10 (60)
Mastalerz[66] 2002	36.2 10/19 (52.6)	Stable	84.3 ±13.5	Placebo ECT 22.5±10.2	NR	11/19 (57.9)	17/19 (89.5)
Pearlman[67] 1999	10.5±2.0 22/39 (56.4)	Stable	89.5±11.4	Placebo ECT 16.7±10.8	Non-smokers	NR	None
Pearlman[68] 2005	24.5±5.9 24/51 (47)	Stable; mild to moderate	86.4±11.9	Placebo ECT 22.3±13.1	NR	NR	6/51 (12)
Peroni[69] 2002	11.1±1.8 13/19 (68)	Stable	87.7±8.7	Placebo ECT 15.3±12.8	NR	19 (100)	19 (100)
Philip[70] 2007a	26.0±7.9 23/47 (48.9)	Mild	87.8±11.4	Placebo ECT 27.8±6.2	Non-smokers	38/47 (81) allergic rhinitis	2/47 (2)
Philip[71] 2007b	24.4±6.9 33/62 (53.2)	Stable; mild to moderate	88.9±12.4	Placebo ECT 17.5±13.8	NR	NR	7 (11)
Rundell[44] 2005	22.8±6.8 8/11 (72.7)	Mild	98.4±14.2	Placebo ECT 22.4±18.0	NR	NR	None

ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; NR = not reported; SD = standard deviation

Table 29. Quality assessment of trials in the therapy review: LTRA

Author Year	Described as randomized?	Described as double-blind?	Description of withdrawals/ dropouts?	Method of randomization described and appropriate?	Method of double-blinding described and appropriate?	Method of randomization described but inappropriate?	Method of double-blinding described but inappropriate?	Overall Score: Jadad	Concealment of allocation
Becker[64] 2002	Yes	Yes	No	No	Yes	No	No	3	Unclear
Coreno[65] 2000	Yes	No	No	No	Yes	No	No	2	Unclear
Mastalerz[66] 2002	Yes	Yes	Yes	No	No	No	No	3	Unclear
Pearlman[67] 1999	Yes	Yes	Yes	No	Yes	No	No	5	Unclear
Pearlman[68] 2005	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Peroni[69] 2002	Yes	Yes	Yes	No	No	No	No	3	Unclear
Philip[70] 2007a	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Philip[71] 2007b	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Rundell[44] 2005	Yes	Yes	Yes	No	No	No	No	3	Unclear

Key Question T–3: Inhaled Corticosteroid Therapy

Description of Included Studies

Four randomized crossover trials[72-75] met the inclusion criteria for the review on the prophylactic use of a single dose of inhaled corticosteroid therapy (ICS) prior to an ECT. The studies were published in peer reviewed journals between 1974 and 2001 and all were conducted in Europe. The definitions of EIA as measured by the FEV_1 percent fall index were 10 percent or greater,[73] 15 percent or greater,[74,75] and 20 percent or greater.[72] The ECT was performed on a treadmill,[73,74] bicycle ergometer,[75] or by having participants run or exercise hard.[72] The characteristics of the trials are summarized in Table 30.

The drugs studied were betamethasone valerate,[72,73] budesonide,[75] and fluticasone propionate.[74] The number of patients enrolled ranged from 9 to 20 (total=50). Two studies[73,74] included children only, one included adults only,[75] and one included both adults and children.[72] All participants had confirmed asthma; for most, their asthma was mild to moderate and stable. The baseline characteristics of the participants are presented in Table 31.

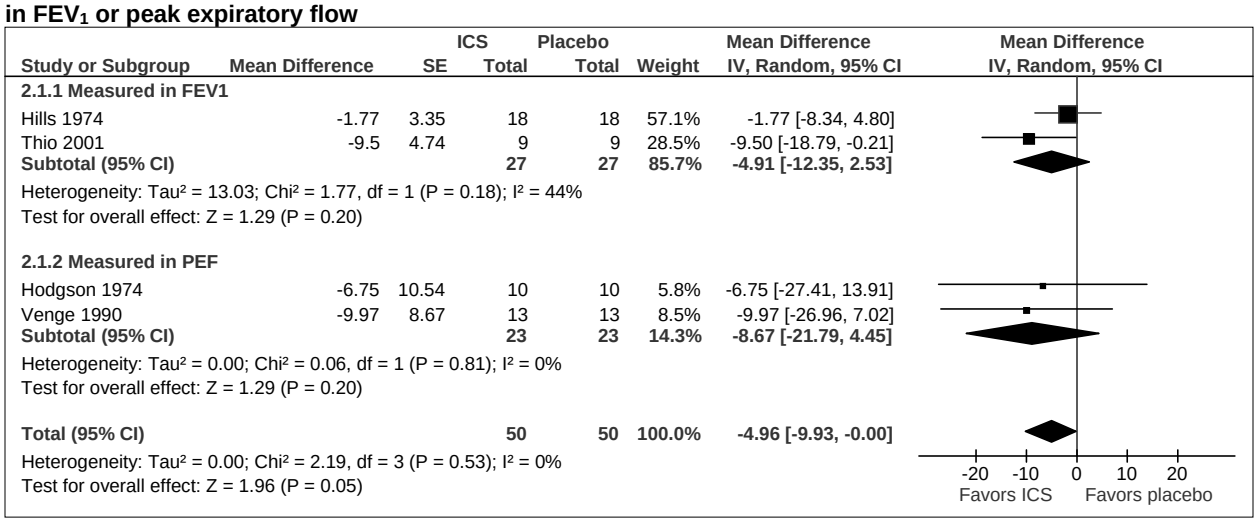
Methodological Quality of Included Studies

Table 32 summarizes the methodological quality of the included studies. Overall, the quality of the four trials was good with a median Jadad score of 3.5 (IQR: 3, 4). Concealment of allocation was unclear in three trials[72,74,75] and inadequately reported in one.[73] One trial did not report their source of funding,[73] two had private industry support,[72,74] and one was supported by a government grant.[75] The body of evidence is classified as "moderate."

Quantitative Results

Pulmonary function measures. Two trials[72,74] reported the maximum percent fall in FEV_1 and two[73,75] reported the maximum percent fall in peak expiratory flow (PEF) post-ECT. The mean fall in FEV_1/PEF on the placebo challenges ranged from 19.2 to 36.2 percent (average 30.5). Three of the placebo groups[72,73,75] had a mean fall in FEV_1/PEF greater than 30 percent indicating moderate to severe EIA. The average fall in FEV_1/PEF in the ICS arms ranged from 9.7 to 31.9 percent (average 25.5). The pooled MD was 5.0 percent (95 percent CI: 0.0, 9.9). The differences were not statistically significant and the results failed to identify important heterogeneity (I^2=0) (Figure 20).

Figure 20. Inhaled corticosteroids vs. placebo in pre-exercise treatment of EIA: MD in maximum percent fall in FEV_1 or peak expiratory flow



Clinical protection. The mean clinical protection over placebo for participants was either reported as an outcome measure or we were able to calculate it from the data. The protection index in children was 49 percent after a high dose of fluticasone,[74] and 19.6 percent after betamethasone.[73] A combined population of children and adults who received betamethasone[72] did better on the placebo (clinical protection was –5.9 percent). The clinical protection index for adults who received budesonide[75] was 27.5 percent.

Complete protection. Thio et al[74] provided IPD from which we could determine that 6 of 9 participants using high dose fluticasone obtained complete protection (maximum percent fall FEV_1 less than 10 percent) compared with 4 of 9 on placebo (RR=1.5; 95 percent CI: 0.6, 3.6). This outcome was not reported in any of the other trials.

Adverse effects. None of the studies reported on adverse events.

Conclusions. We cannot conclude that ICS taken prior to exercise provides a clinical benefit to people with stable asthma who experience EIA.

Table 30. Description of trials in the therapy review: Inhaled corticosteroids

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Treatment Groups: drug; dose; delivery device; time pre-ECT (min)	ECT: type; duration; % predicted HR temp; RH; Study days; challenges/day [N]; time between challenges Withheld asthma med; class; time	Definition EIA/EIB (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Hills[72] 1974 United Kingdom Clinic	Journal article Glaxo Ltd. Crossover	20 18 2	BV: 0.2 mg; MDI; 15 min P: NA; MDI; 15 min	Ran or exercised sufficiently to maintain a steady level of dyspnoea; NR NR; NR 3; 1 1-2 d BD x 6-9 hr	≥20% Primary: FEV_1 L Secondary: max% fall FEV_1; mean % fall FEV_1; clinical protection FEV_1 measured at 5, 10, 15, 20 min post ECT NR
Hodgson[73] 1974 United Kingdom Clinic	Journal article NR Crossover	10 10 0	BV: 0.2 mg; MDI; immediately before P: NA; MDI; immediately before	Treadmill; HR ≥160 bpm NR; NR 4; 1 NR but all at same time of d All x 12 hr	≥10% Primary: mean % fall PEF Secondary: clinical protection PEF measured at 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40 min post ECT NR
Thio[74] 2001 Netherlands Clinic	Journal article GlaxoWellcome Netherlands Crossover	9 9 0	FP: 1 mg; MDI with spacer 4 hr P: NA; MDI with spacer; 4 hr	Treadmill; 90% of predicted maximum NR; NR 2; 1 7-14 d BD x 12 hr; cromoglycates x 2 wk	≥15% Primary: mean % fall FEV_1 Secondary: % protection; clinical protection FEV_1 measured at 1, 3, 6, 9, 12, 15, 20, 25, 30 min post ECT NR
Venge[75] 1990 Sweden Clinic	Journal article Government Crossover	13 13 0	BUD: 1 mg; MDI; 15 min P: 5 puffs; MDI; 15 min	Bicycle ergometer; 80% NR; absolute humidity=5.85±1.72; 2; 1 NR CS x 3 mo; BD/SCG; oral BD x 8 hr and 24 hr	>15% Primary: max % fall PEF Secondary: clinical protection PEF measured at 1, 3, 5, 10, 15, 20, 25, 30, 60 min post ECT; NR

BD = bronchodilator; bpm = beats per minute; BUD= budesonide; BV= betamethasone valerate;CS=corticosteroids; d = day(s); ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; FP= fluticasone propionate; hr = hour(s); HR = heart rate; L = liter; MDI = metered dose inhaler; min = minute(s); mg = milligram; mo = month(s); NR = not reported; P = placebo; PEF = peak expiratory flow; RH = relative humidity; SCG = sodium cromoglycate; temp = temperature; wk = week(s)

Table 31. Baseline characteristics of patients in trials in the therapy review: Inhaled corticosteroids

Author Year	Age yr (mean±SD) Males: N (%)	Asthma status	Pulmonary function (% predicted FEV_1 (mean±SD)	Max % fall FEV_1 (mean±SD)	Smoking status: N (%)	Atopic status: N (%)	ICS history: N (%)
Hills[72] 1974	Range 5-30 9/18 (50)	5=mild; 10=moderate; 3=severe	2=normal; 3=76-90%; 10=51-75%; 3 >50%	Control ECT 49%	NR	16/18 (89)	None
Hodgson[73] 1974	Children NR	Stable	>50% predicted PEF	Control ECT 35% (PEF)	NR	NR	None
Thio[74] 2001	11.2±2.5 6 (67)	Mild to moderate (ATS)	102 ±11.8	Placebo ECT 19.2±17.3	NR	NR	None
Venge[75] 1990	29.2±8.3 7 (53.8)	Stable	84.8±11.9 (PEF)	Control ECT 36.2±13.6	NR	9/13 (69.2)	None

ATS = American Thoracic Society; ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; NR = not reported; PEF = peak expiratory flow; SD = standard deviation; yr = year

Table 32. Quality assessment of trials in the therapy review: Inhaled corticosteroids

Author Year	Described as randomized?	Described as double-blind?	Description of withdrawals/ dropouts?	Method of randomization described and appropriate?	Method of double-blinding described and appropriate?	Method of randomization described but inappropriate?	Method of double-blinding described but inappropriate?	Overall Score: Jadad	Concealment of treatment allocation
Hills[72] 1974	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Hodgson[73] 1974	Yes	Yes	Yes	No	Yes	No	No	4	Inadequate
Thio[74] 2001	Yes	Yes	Yes	No	No	No	No	3	Unclear
Venge[75] 1990	Yes	Yes	Yes	No	No	No	No	3	Unclear

Key Question T–4: Mast Cell Stabilizers

Background

With better understanding of the possible role of inflammatory mediators and mast cell degranulation in the pathogenesis of EIB/EIA, a variety of mast cell degranulation drugs have been investigated for their potential to protect against bronchoconstriction caused by exercise. Sodium cromoglycate (SCG; also referred to as "cromolyn sodium") and nedocromil sodium (NCS) are mast cell stabilizer (MCS) agents introduced in the late 1960s and early 1980s, respectively. Both are reportedly effective on a single-use basis for inhibiting bronchoconstriction due to antigens, fog, cold air, sulphur dioxide, and exercise. If effective and safe in EIB/EIA, these properties would make them attractive therapeutic options for active people.

During preliminary searches of the literature on MCS, three systematic reviews were identified. All three were published in the Cochrane Library and two were subsequently published in peer-reviewed journals. The reviews addressed the following topics: NCS to prevent EIA,[76,104] NCS versus SCG to prevent EIA,[77] and MCS versus an anticholinergic agent, a SABA agent, or a combination of MCS and SABA agents to prevent EIA.[78] Our search strategy included terms to locate any new or additional RCTs that would add to the existing reviews. None were identified (Appendix E).

SCG is no longer available in a dry-powdered inhaler in North America; the only remaining formulations for asthma are solutions for nebulization. The evidence related to these drugs in EIB/EIA are summarized from the existing reviews.

NCS versus Placebo Review

Design issues. All the studies included in this review were randomized crossover trials.[76,104] The ECTs were conducted on separate days and the researchers adhered to the recommended washout time of 5 to 10 times the half-life of a drug between challenges.

Objective. The objective of the review was to compare the effects of a prophylactic dose of inhaled NCS with placebo in persons with confirmed EIA. The primary outcome was a measure of the change in the percent fall index pre- or post-exercise. Secondary outcomes were the mean percent fall in FEV_1 at varying time points up to 1 hour post-ECT and the degree of clinical protection afforded by NCS over placebo. A mean protection index of 50 percent or more was considered clinically significant. The review also investigated subgroups based on dose, delivery device, timing of pre-treatment, severity of EIA, and age.

Populations. Recruitment procedures were not often described but generally seemed to be volunteers from asthma clinics or schools for asthmatic children. All had documented asthma and demonstrated reproducible EIA. All were described as having stable asthma at testing, were otherwise healthy, non pregnant, and had no respiratory comorbidity.

Exercise challenge tests. All ECTs were conducted indoors on an inclined treadmill (n=18), a bicycle ergometer (n=1), FRAST (n=1), or sport specific (n=1) (3 sprinters ran outdoors). Room temperatures ranged from 17 to 24 degrees Celsius and relative humidity ranged from 35 to 60 percent. One trial[163] conducted a trial using cold air (-18 degrees Celsius). Regardless of the challenge format, the intensity and duration demanded was sufficient to induce EIA.

Results. *Description of studies*. There were 21 RCTs included in the review (20 peer reviewed articles and one unpublished thesis). The trials all used the crossover design but did not report data by period and only one reported the treatment sequence. The reviewers analyzed the

data as though from parallel studies determining that this approach would provide a more conservative estimate of treatment effect. Data on continuous measures were pooled and reported as MD with 95 percent CI using a random effects model. In the subgroup analyses examining the effect of treatment based on baseline severity, mild EIA was defined a priori as a mean maximum percent fall in FEV_1/PEF less than 30 percent on the placebo challenge. Moderate to severe EIA was defined as a mean maximum percent fall greater than 30 percent.

Methodological quality. Using the Jadad scale for RCTs, two studies were rated "strong" (5 points), nine "very good" (4 points), with the remaining 10 studies rated as "good" (3 points). All studies were double-blinded. Two studies were rated as "adequate" concealment of allocation; the remaining studies were rated "unclear." The body of evidence is classified as "moderate."

Pulmonary function results. Seventeen trials measured the FEV_1 to determine the response to treatment following an ECT (total sample size=240; 11 children and 6 adult studies); seven measured the PEF (total sample size=115; 4 children and 3 adult studies). Three trials assessed the duration of effect over two or three challenges given 2 to 4 hours apart on the same day.

The maximum percent fall in either FEV_1 or PEF improved significantly following NCS indicating a statistically and clinically significant attenuation of the EIA response over placebo (MD =15.6 percent; 95 percent CI: 13.2, 18.1) (Table 33). Subgroup analyses indicated no significant differences: age (children less than 18 years; n=11), dose (low less than 4 mg, n=3; standard 4 mg, n=16; high more than 4mg, n=1), delivery system (metered dose inhaler [MDI], n=12 versus MDI with spacer device, n=5), and timing of pre-treatment (less than 30 minutes, n=10 versus 30 minutes or more, n=7). The effect of NCS appeared more pronounced in those that experienced moderate to severe EIA (i.e., a fall index 30 percent or more). In this the MD increased to 21.36 percent (95 percent CI: 25.52, 17.20).

Other outcomes. Thirteen studies compared lung function up to 30 minutes post-challenge. At each of seven time points pre-treatment with NCS resulted in significant improvements in FEV_1 and a return to within 10 percent of baseline function occurred in 10 minutes compared with 30 minutes with placebo.

In three trials that examined the duration of action on subsequent ECTs within 4.5 hours on the same day with no further medication, NCS appeared to offer benefit but of a lesser magnitude (MD=5.7 percent; 95 percent CI: 2.8, 14.2).

The trials provided no data on symptom scores, performance measures or participant preference. Subgroup comparisons by sex and corticosteroid use were not performed due to lack of data. Sensitivity analyses based on study quality, fixed versus random models, and publication status were all nonsignificant.

Adverse events. Twelve studies mentioned side effects. Seven stated that no adverse effects or symptoms attributable to NCS were observed. Minor effects reported were bad taste, throat irritation, and cough, and in one study a clinically insignificant increase in heart rate of four beats per minute.

Conclusions. In people with stable asthma that experience EIA, NCS taken 15 to 60 minutes prior to exercise reduces the severity and duration of EIA in both children and adults. The benefit appears more pronounced in those with more severe EIA.

NCS versus SCG Review

Design issues. Only crossover trials were included in this revew.[77,161] To ensure drug clearance, the challenges within each study were conducted with a minimum 24 hour break.

Objective. The objective of the review was to compare the effects on post-exercise lung function following prophylactic doses of NCS and SCG by MDI, in persons with confirmed EIA. The primary outcome was the maximum percent fall index. The review also reported the odds ratio (OR) and 95 percent CIs of *not* obtaining complete protection and clinical protection over placebo. Complete protection was not obtained if the post-exercise fall in FEV_1 exceeded either the 10 or 15 percent diagnostic cutpoints. Clinical protection was not obtained if the post-exercise fall in FEV_1 after NCS or SCG was less than 50 percent of the drop following placebo.

Population. Recruitment procedures were not well described but appeared to be healthy volunteers from either asthma clinics or schools for asthmatic children. Five studies involved children (6.5 to 15 years), three involved adults (17 to 38 years), and one study enrolled a mixed population (13 to 30 years). The majority recruited stable asthmatics with a reproducible post-exercise fall in FEV_1 of either 15 percent or 20 percent.

Exercise challenge tests. All ECTs were performed indoors on either an inclined treadmill (n=8) or a bicycle ergometer (n=1) for a duration of 6 to 8 minutes. Intensity required was reported as either a heart rate of 170 to 180 or 85 percent of predicted maximum for age. ECTs were conducted in controlled environments; however, room temperature and humidity were not reported. In all studies, the ECTs were conducted at the same time of day on different days.

Results. *Description of studies.* The review included nine RCTs (eight peer-reviewed articles and one conference abstract). As in the previous review, the data were analyzed as though they were from parallel studies. Data on continuous measures were pooled and reported as a MD with 95 percent CI, using a random effects model. Dichotomous variables for individual and pooled statistics were calculated as OR with 95 percent CI, using a random effects model. We have converted the OR of *not* obtaining complete or clinical protection to the RR of obtaining complete or clinical protection to allow comparisons to the key questions from the current review.

Subgroup analyses were performed on adults (18 years and older) versus children (under 18 years), baseline asthma severity (mild versus moderate-severe), different doses of NCS and SCG, and the timing of ECT post-treatment.

Methodological quality. Using the Jadad scale one study was rated “strong” (5 points), one “very good” (4 points), with the remaining studies rated as “good” (3 points). All studies except one were double-blinded. One study was rated as “adequate” concealment of allocation; the remaining studies were rated “unclear.” The body of evidence is classified as “moderate.”

Pulmonary function results. Seven trials reported the maximum percent fall in FEV_1 (sample size=97; 5 children, 2 adult studies). No significant differences between NCS and SCG were identified (MD=-0.88; CI: -4.50, 2.74; $I^{2=}$0 percent). Subgroup analyses based on dose (NCS 4 mg versus SCG 10 mg, n=5; NCS 4 mg versus SCG 20 mg, n=1; NCS 8 mg versus SCG 4 mg, n=1) and timing of the ECT (30 minutes or less, n=7; 120 to 140 minutes, n=2; 240 minutes, n=1) failed to identify significant differences (Table 33).

Other outcomes. Six trials reported complete protection using a fall in FEV_1 of less than 10 percent and six used less than 15 percent; six also reported clinical protection over placebo. There were no significant differences between NCS and SCG by diagnostic cutpoint in providing complete or clinical protection (Table 33). The trials provided no data on symptom scores, performance measures or participant preference.

Adverse events. Three trials reported on treatment side effects (unpleasant taste N=3; sore throat N=2). No significant differences were found between NCS and SCG with respect to

unpleasant taste (RR=3.77; 95 percent CI: 1.29, 10.97) or sore throat (RR=4.96; 95 percent CI: 20.1, 9.1). Overall, the trend in both cases was for fewer side effects in the SCG group.

Conclusions. In people with stable asthma who experience EIA, both NCS and SCG provide a significant protective effect against EIA. No significant differences were evident between the two drugs on pulmonary function; however, more people experienced a sore throat or an unpleasant taste from NCS.

MCS to Prevent EIA Review

Design issues. This review[78] was restricted to full manuscripts regardless of publication status and three foreign language studies were included. All but two studies used a crossover design.

Objective. The objective of the review was to compare the effects of a prophylactic dose of either NCS or SCG (collectively called MCS) to that of atropine, ipratropium or oxitropium bromide (collectively called anticholinergics), and SABA. The review also compared the effects of a combination of SABA plus MCS to a SABA alone. The primary outcome was the percent fall in FEV_1 post-exercise. The review also reported the OR and 95 percent CIs of obtaining complete protection and clinical protection. Complete protection was obtained if the post-exercise fall in FEV_1 was less than either the 10 or 15 percent diagnostic cutpoints. Clinical protection was obtained if the post-exercise fall in FEV_1 after drug intervention was at least 50 percent less than that with placebo.

Population. Recruitment procedures were not well described but appeared to be healthy volunteers from either asthma clinics or schools for asthmatic children. Thirteen trials recruited children (6 to 13 years) and 11 recruited adults (18 years and older). Most studies documented recruiting healthy, stable, asthmatics and all of the trials required at least a 15 percent fall in FEV_1 to diagnose EIA. The populations in seven trials were considered to have mild EIA defined as a percent fall index less than 30 percent on placebo; 16 were classified moderate to severe; one did not report baseline data.

Exercise challenge tests. The ECTs involved an inclined treadmill (n=19), FRAST (n=1), bicycle ergometer (n=3), and stair climbing (n=1). Most studies reported an exercise challenge time of between 5 to 8 minutes with a target heart rate ranging from 150 to 180 beats per minute.

Results. *Description of studies.* The 24 RCTs included in the review reported data on 518 participants. The studies compared the following drug combinations: MCS versus anticholinergics (8 studies), MCS versus SABA (20 studies), and SABA versus a combination of SCG plus SABA (10 studies). The method of delivery varied across studies (8 nebulizer, 5 MDI, 3 spinhaler, and 2 not described), with six studies comparing two or more devices. 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.

Methodological quality. Using the Jadad score, two studies were rated “strong” (5 points), five rated “very good” (4 points), nine rated “good” (3 points), and eight rated “poor” (2 points or less). Four studies were rated to have “adequate” concealment of allocation; the rest were rated “unclear.” The body of evidence is classified as “moderate.”

Pulmonary function results. Sixteen studies (9 children, 7 adult) reported the response to treatment using different FEV_1 measures (maximum percent fall FEV_1=14 studies; percent predicted=1 study; change=1 study); 8 studies (5 children, 3 adult) reported maximum percent fall PEF.

MCS versus anticholinergics: MCS provided a modest but significant advantage in post-exercise lung function over anticholinergics. Pooled results indicate MCS attenuated the fall in FEV_1 to 7.1 percent compared with 13.8 percent on anticholinergics (MD=6.7 percent; 95 percent CI: 3.3, 10.0; I^2=0 percent). MCS provided more individuals with complete protection (OR=2.2; 95 percent CI: 1.3, 3.7) and clinical protection (OR=2.7; 95 percent CI: 1.1, 6.4). There were no subgroup differences based on age, severity, or study quality. No adverse effects were reported for either agent group.

MCS versus SABA: When compared with SABA, MCS were not as effective at preventing EIA. The mean maximum percent fall in FEV_1 using MCS was 11.2 percent compared with 4.3 percent on SABA (MD=6.8 percent; 95 percent CI: 4.5, 9.2; I^2=20 percent).). MCS provided fewer individuals with complete protection (OR=0.3; 95 percent CI: 0.2, 0.5) or clinical protection (OR=0.4; 95 percent CI: 0.2, 0.8). There were no significant subgroup differences based on age, severity, drug, delivery, or study quality.

SABA versus combination of SCG plus SABA: Combining a MCS with a SABA did not indicate significant advantages to pulmonary function over SABA alone. On average the maximum fall in FEV_1 on SABA alone was reduced to 5.3 percent compared with 3.5 percent using a combination (MD=1.3 percent; 95 percent CI: -6.3, 8.9). There were no significant differences in the number achieving complete protection (OR=0.5; 95 percent CI: 0.2, 1.4) or clinical protection (OR=0.4; 95 percent CI: 0.1 to 1.2). There were no subgroup differences. Overall, every comparison favored the combination; however, none reached statistical significance.

Other outcomes. One study measured the work effort involved during exercise. This analysis showed that SCG and SABA significantly decreased the energy cost of running, ventilation, oxygen consumption, and tidal volume which significantly increased running duration. The trials provided no data on symptom scores, performance measures or participant preference.

Adverse events. A nonsignificant difference in side effects was demonstrated with 11 percent of SABA patients experiencing side effects compared with 3 percent of those receiving MCS (OR=0.2; 95 percent CI: 0.0, 8.2). No adverse events were reported for MCS versus anticholinergics or SABA versus combinations of MCS and SABA.

Conclusions. In people with stable asthma who experience EIA, SABA, MCS, and anticholinergic agents can provide a significant protective effect against EIA with few adverse effects. On average, SABA agents were more effective than MCS, and MCS agents were more effective than anticholinergics. The combination of SABA and MCS agents did not provide significant advantages over a SABA alone; however, this approach may be appropriate for some people.

Table 33. Description of trials included in the Cochrane reviews of mast cell stabilizers

Author Year Number of trials included Country Dates published (range)	Publication status # of trials Children [C], Adults [A] Funding Trial design	Randomized [R] Sample size range [SS] Analyzed [A] Withdrawals [W]	Inclusion criteria	Intervention: drug; dose; delivery device Time pre-ECT Comparison	ECT: type Withheld asthma med	Definition EIA (% fall FEV_1)	Outcomes: Primary Secondary Adverse events (N=studies)
Spooner[76,104] 2002 N=21 (20 in the MA) North America=1, Europe=18, Australia=2 1987-1995	20 journal articles; 1 unpublished thesis C: N=11 A: N=10 Funding NR All crossover trials	R=280 SS=8-24 (mean 14) A=279 W=1	Reproducible EIA Stable asthma Lung function >70% predicted; variability between challenges <10-15% N=1 Olympic athletes N=20 physical conditioning NR	NCS: 1 mg, N=1; 2 mg, N=3; 4 mg, N=20; 8 mg, N=2 MDI, N=21; MDI plus spacer, N=5 Time pre-ECT 15 min, N=3; 20 min, N=8; 30 min, N=9; 60 min, N=1; 120-150 min, N=3; 240-270 min, N=2 Placebo	Inclined treadmill N=17; FRAST N=1; Bicycle ergometer N=1; Sport specific N=1 All asthma meds stopped appropriately for 6 h to 1 wk; some allowed ICS to continue	Max % fall FEV_1 or PEF ≥15% N=11 ≥20%: N=9	Primary: mean max % fall: FEV_1, N=17; PEF: N=7 Secondary: clinical protection (≥50%); mean % protection; time course analysis AE reported in 12/20 trials; 7/12 none observed; 5/12 reported bad taste, throat irritation, cough
Kelly[77,161] 2000 N=9 (8 in the MA) North America=1; Europe=7; Australia=1 1987-1995	8 journal articles; 1 abstract C: N=5 A: N=3 Mixed N=1 Funding NR All crossover trials	R=162 SS=8-45 A=162 W=unclear	Hx EIA Stable asthma Atopic Baseline FEV_1 >70% predicted, and vary <10% from previous study day No URIs in last 3 wk Non-smokers	NCS: 4 mg, N=7; 8 mg, N=1 SCG: 4 mg, N=1; 10 mg, N=6; 20 mg, N=1; dose NR, N=1 MDI N=8; MDI plus spacer N=4 Time pre-ECT 15 min, N=1; 20 min, N=5; 30 min, N=2; 120 min, N=1;140 min, N=1; 240 min, N=1	Inclined treadmill: N=8 Most meds stopped appropriately for 4 hr to 1 wk; some allowed ICS to continue	Max % fall FEV_1 or PEF ≥15% N=7; ≥20% N=1; NR N=1	Primary: mean max % fall: FEV_1 N=7 Secondary: clinical protection N=5; complete protection N=7 AE reported in 3/8 trials; 1/3 none observed; 2/3 observed unpleasant taste, throat irritation

AC = anticholinergic; AE = adverse events; BD = bronchodilator; ECT = exercise challenge test; EIA = exercise-induced asthma; Fen = fenoterol; FEV_1 = forced expiratory volume in 1 second; FRAST = free running asthma screening test; hr = hour(s); Hx = history; MA = meta analysis; max = maximum; MCS = mast cell stabilizers; MDI = metered dose inhaler; min = minute(s); mg = milligram; NCS = nedocromil sodium; NR = not reported; PEF = peak expiratory flow; SABA = short-acting beta-agonist; Sal = salbutamol; SCG = sodium cromoglycate; URI = upper respiratory infection; wk = week(s)

Table 33. Description of trials included in the Cochrane reviews of mast cell stabilizers (continued)

Author Year Number of trials included Country Dates published (range)	Publication status Children [C], Adults [A] Funding Trial design	Randomized [R] Sample size range [SS] Analyzed [A] Withdrawals [W]	Inclusion criteria	Intervention: drug; dose; delivery device Time pre-ECT Comparison	ECT: type Withheld asthma med	Definition EIA (% fall FEV_1)	Outcomes: Primary Secondary Adverse events (N=studies)
Spooner[78] 2003 24 North America =3; Europe =17; Asia=2; Australia=2 1976-1998	24 journal articles C: N=13 A: N=11 Funding NR Crossover: N=22; Parallel: N=2	R=518 SS=7-100 A=505 W=5 trials reported total of 13 withdrawals	Hx of asthma and/or EIA CS oral and inhaled use varied (never, none in past 2 mo., or currently taking) Lung function >50% predicted; variability between challenges <10-15%	MCS N=24 SCG N=23, 2-40 mg NCS: N=1, 4 mg AC N=11 IB: N=8, 0.12–2 mg Atropine: N=2, 0.2% OB: N=1, 0.02 mg MCS vs. AC N=11 SCG vs. SABA N=20; Fen N=6, 0.1–2 mg Sal N=10, 0.2-2.5mg Terbutaline N=2 Reproterol, procaterol, isoproterenol N=1 each SCG vs. SCG plus SABA N=10 Combination doses SCG 1–20mg; Fen N=4, 0.05–0.4 mg Sal N=3, 0.2–2.5mg Terbutaline N=1, 0.5mg Reproterol N=1, 1.0mg Device Nebulizer N=8; MDI N=5; spinhaler N=3; NR N=2; ≥2 devices N=6 Time pre-ECT 10 min N=4; 15 min N=6; 15-45 min N=1; 20 min N=3; 30 min N=6; 30-45 min N=1; 60 min N=2; 120 min oral N=1	Inclined treadmill: N=19 FRAST: N=1 Bicycle ergometer: N=3 Stair climbing: N=1 Most meds stopped for 8 h to 1 wk; some allowed ICS to continue; 1 did not permit any meds throughout the trial	Max % fall FEV_1 or PEF ≥10% N=1 ≥15% N=5 ≥20% N=13 ≥25% N=1 ≥30% N=1 NR=3	Primary: FEV_1 (N=16); max % fall N=14; % predicted N=1; change N=1; max % fall PEF N=8 Secondary: complete protection; clinical protection AE reported in 11/24 trials; 7/11 none observed; 2/7 tremor and distress/agitation on SCG or fenoterol; 1/7 mild throat irritation on SCG

Table 34. Baseline characteristics of patients in trials included in the Cochrane reviews of mast cell stabilizers

Author Year	Age yr (mean±SD) Males: N (%)	Asthma status	Pulmonary function (% predicted FEV_1 / mean±SD)	Max % fall FEV_1 (mean±SD)	Smoking status: N (%)	Atopic status: N studies	ICS history N (%)
Spooner[76] 2002	C: 11.3±2.2 A: 26.5±5.0 M ~ 64% Not all reported male/female mix	All stable at time of ECT	FEV_1 >70% predicted; variability <10-15% between challenges	Mean range of EIA severity on control or placebo ECT C: 28.7 to 50.0% A: 15.00 to 40.6% Mean fall <30% N=16 Mean fall ≥30% N=5	Nonsmokers N=3; NR N=17	All atopic N=12; Mixed/NR N=8	None on ICS N=7; mixed/NR=23
Kelly[77] 2002	C:11.85±4.4; A: 24±4.2 M ~ 54% Not all reported male/female mix	All stable at time of ECT	FEV_1 >70% predicted; variability <10-15% between challenges	Mean range of EIA severity on control or placebo ECT C: 27.4 to 35.9% A: 15.00 to 33.2% Mean fall <30% N=4 Mean fall ≥30% N=4 NR N=1	Nonsmokers N=1; NR N=8	All atopic N=3; mixed/NR N=8	None N=4; mixed/NR N=5
Spooner[78] 2003	C:11.49±3.99 A: 26.98±11.15 M ~ 48% Not all reported male/female mix	All stable at time of ECT	FEV_1 >70% predicted; variability <10-15% between challenges	Mean range of EIA severity on control or placebo ECT C: 14.3 to 45.2% A: 15 to 47% Mean fall <30% N=7 Mean fall ≥30% N=16 NR N=1	Nonsmokers N=4; 3/18 smokers included N=1 ; NR N=19	2/49 atopic N=1; all atopic N=1; NR N=22	Unclear N=6; mixed N=4; steroid use an exclusion criteria N=9

A = adult; C = children; ECT = exercise challenge test; EIA = exercise-induced asthma; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; M = males; NR = not reported; SD = standard deviation

Key Question T–5: Anticholinergic Agents

Description of Included Studies

Eighteen randomized crossover trials[79-96] met the inclusion criteria for the review of short-acting anticholinergic (SAAC) therapy. The studies were published between 1976 and 1989. All studies were conducted either in Europe[79,82,85-90,92-94] or North America.[80,81,83,84,91,95,96]

The drugs studied were atropine,[84,86,91] ipratropium bromide (IB),[79-83,85,87,88,90,93-96] and oxitropium bromide (OB).[88,89,92] The definitions of EIA as measured by the percent fall in FEV_1 or PEF were 10 percent or greater,[81,86,96] 15 percent or greater,[80,83,87-89,91,95] and 20 percent or greater.[79,85,92,93] The ECT was performed on a treadmill,[79,83-86,89,90,92-94,96] bicycle ergometer,[80,81,87,88,91,95] and free running (FRAST).[82] The characteristics of the trials are summarized in Table 35.

The baseline characteristics of the participants are presented in Table 36. The number of patients enrolled ranged from 6 to 20. Seven studies[79,80,84,86,89,91,96] included only children, eight included only adults, [81-83,87,88,90,94,95] and three included both.[85,92,93] All participants in these trials had a confirmed asthma status; for most, the asthma was mild and stable.

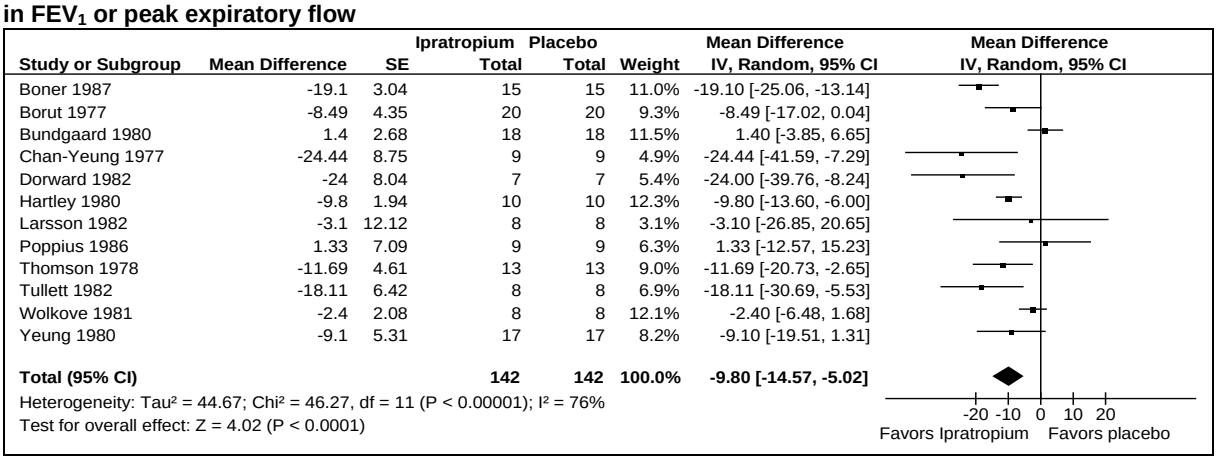
Methodological Quality of Included Studies

Table 37 summarizes the methodological quality of the included studies. Overall the quality of the 18 trials was low with a median Jadad score of 2.5 (IQR: 2, 3) (Table 37). Concealment of allocation was unclear in all the trials. Seven trials did not report their source of funding,[79,82,85,86,91,92,94] eight received private industry support,[80,83,87-90,93,95] and three were supported by government grants.[81,84,96] The body of evidence is classified as "moderate."

Quantitative Results

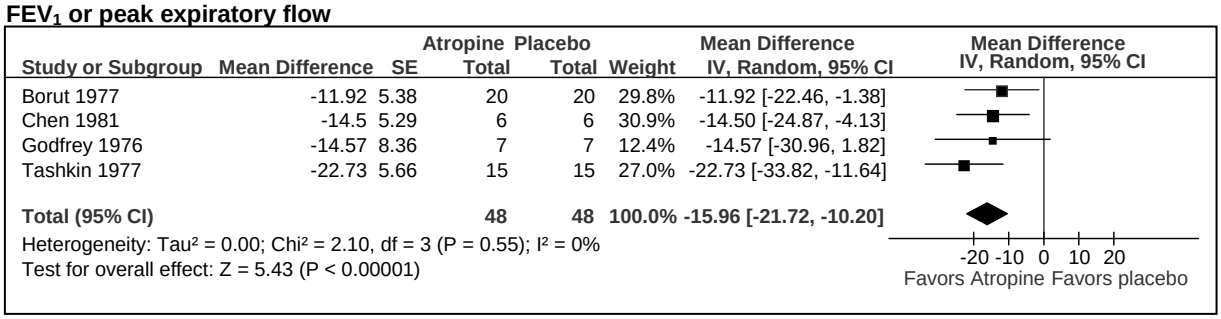
Pulmonary function measures. Eleven trials compared IB to placebo[79,80,83,85,87,88,90,93-96] and reported the maximum percent fall in FEV_1 as the outcome measure; one[82] reported the maximum percent fall in peak expiratory flow (PEF). The mean fall in FEV_1/PEF on the placebo challenges ranged from 14 to 41 percent (average 32). Seven of the placebo groups[79,83,85,88,90,93,96] had a mean fall in FEV_1/PEF greater than 30 percent indicating they experienced moderate to severe EIA. The average fall in FEV_1/PEF in the SAAC arms ranged from 10 to 33 percent (average 21). The pooled difference favored IB over placebo (MD = 9.8 percent; 95 percent CI: 5.0, 14.6) was statistically significant (Figure 21); however, substantial heterogeneity (I^2=76 percent) was identified.

Figure 21. Ipratropium vs. placebo in pre-exercise treatment of EIA: Mean difference in maximum percent fall in FEV_1 or peak expiratory flow



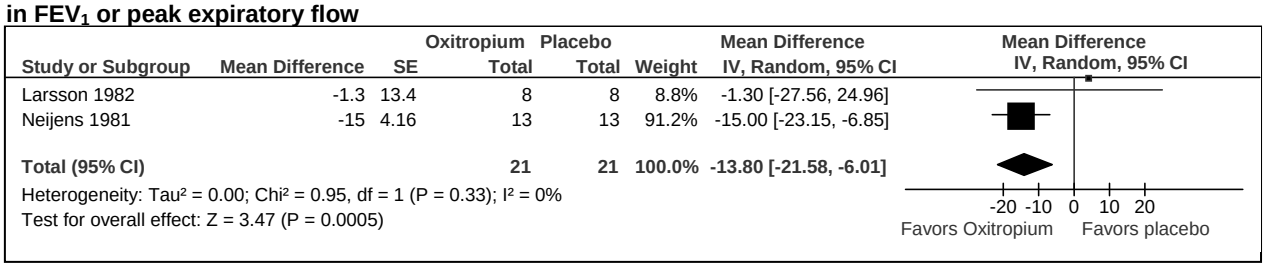
Four trials compared atropine to placebo[80,84,86,91] and all reported the maximum percent fall in FEV_1 as the outcome measure. The mean difference in the percent fall in FEV_1 ranged from 11.9 to 22.7 percent. The pooled estimate indicated that atropine was significantly more effective than placebo in attenuating EIA (MD=16.0; 95 percent CI: 10.2, 21.7) (Figure 22). Negligible heterogeneity was identified (I^2=0 percent).

Figure 22. Atropine vs. placebo in pre-exercise treatment of EIA: Mean difference in maximum percent fall in FEV_1 or peak expiratory flow



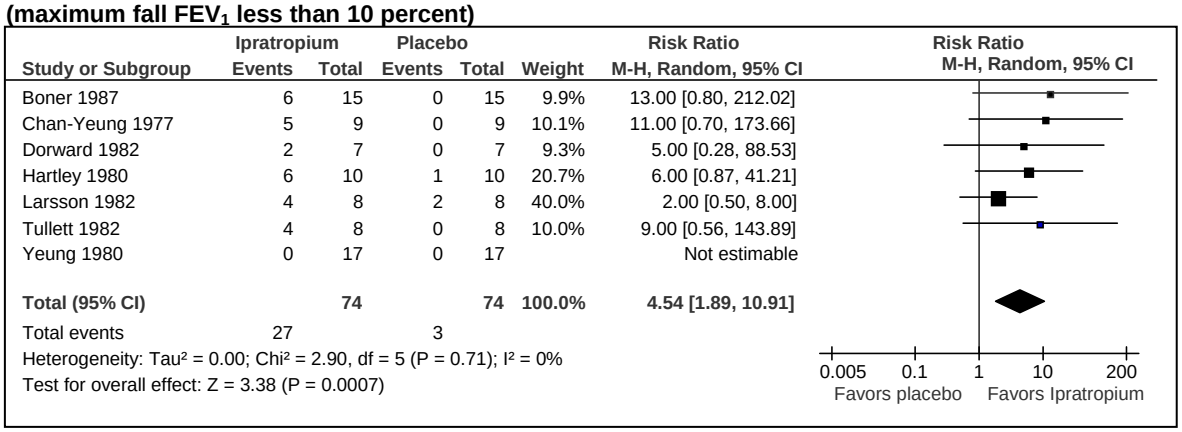
Two trials compared OB to placebo[88,89] and both reported the maximum percent fall in FEV_1 as the outcome measure. The pooled results showed that OB was significantly more effective than placebo in attenuating EIA (MD=13.8; 95 percent CI: 6.0, 21.6) (Figure 23). Negligible heterogeneity was identified (I^2=0 percent).

Figure 23. Oxitropium vs. placebo in pre-exercise treatment of EIA: Mean difference in maximum percent fall in FEV_1 or peak expiratory flow



Complete protection. Seven trials involving IB reported complete protection as an outcome measure.[79,83,85,87,88,94,96] The proportion of patients who achieved complete protection ranged from 0 to 13 percent. The pooled estimate showed that patients are 4.5 times more likely to achieve complete protection with IB compared with placebo (RR=4.5; 95 percent CI: 1.9, 10.9) (Figure 24). Negligible heterogeneity was identified (I^2=0 percent).

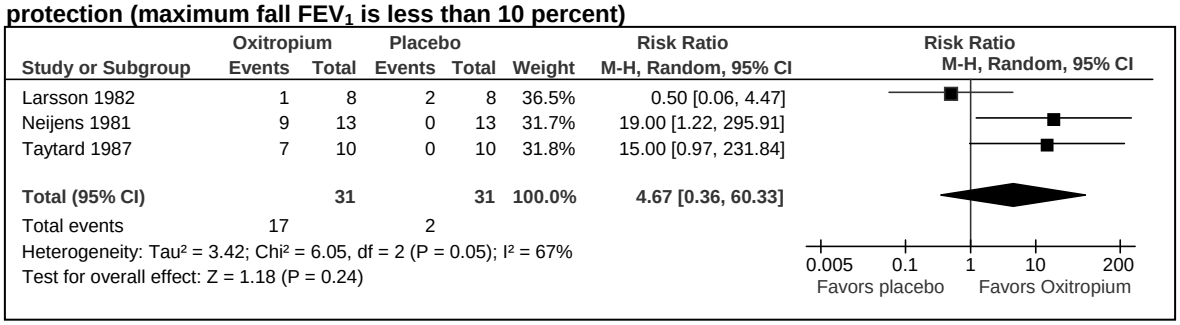
Figure 24. Ipratropium vs. placebo in pre-exercise treatment of EIA: Achievement of complete protection (maximum fall FEV_1 less than 10 percent)



Godfrey et al.[86] found no significant difference in achieving complete protection in patients who received atropine versus placebo (RR=5.0; 95 percent CI: 0.3, 88.5). The remaining studies on atropine did not report this outcome.

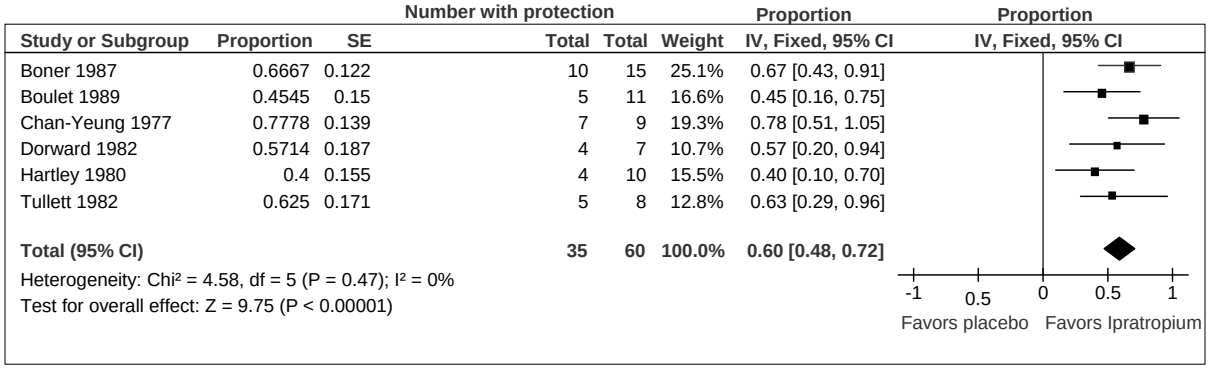
The pooled estimate of RR for complete protection from the three studies[88,89,92] comparing OB with placebo was nonsignificant (RR=4.7; 95 percent CI: 0.4, 60.3) (Figure 25). There was substantial heterogeneity (I^2=67 percent).

Figure 25. Oxitropium bromide vs. placebo in pre-exercise treatment of EIA: Achievement of complete protection (maximum fall FEV_1 is less than 10 percent)



Clinical protection. Six trials that examined IB reported clinical protection as an outcome measure.[79,81,83,85,87,94] The pooled estimate showed that 60 percent (95 percent CI: 48, 72) of patients achieved clinical protection when defined as at least a 50 percent improvement in FEV_1 over placebo (Figure 26). There was negligible heterogeneity (I^2=0 percent).

Figure 26. Ipratropium vs. placebo in pre-exercise treatment of EIA: Achievement of clinical protection (50 percent or greater improvement over placebo in FEV_1)



In the study by Godfrey et al.[86] 29 percent (95 percent CI: 8, 64) of patients achieved clinical protection when taking atropine. The remaining studies did not report on this outcome or provide data for calculation.

Adverse effects. Overall, IB was well tolerated with seven studies reporting no adverse effects.[79,82,87,88,93-95] Dry mouth or thirst was reported in three studies: 16 percent of patients in two studies in which the dose was 0.04 mg of IB,[80,96] and 20 percent at a dose of 0.2 mg and 60 percent at a dose of 2 mg in the third study.[90] Other side effects included bitter taste[90] and slight tremor.[96]

Larsson et al. reported no side effects with oxitropium.[88] The remaining two studies did not report on adverse effects. None of the studies that examined atropine reported on adverse effects.

Subgroup/sensitivity analyses. Subgroup analyses based on age suggest similar results for children and adults for maximum percent decrease in FEV_1. Analyses based on asthma severity did not reduce heterogeneity. Sensitivity analysis on high versus low quality studies did not reduce the heterogeneity.

Table 35. Description of trials in the therapy review: Anticholinergic therapy

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Intervention: drug; dose; delivery device; time pre-ECT	ECT: type; duration (min); % predicted HR Temp; RH; Study days; challenges/day [N]; Time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Boner[79] 1987 Italy Residential home for asthmatics	Journal article NR Crossover	15 15 0	IB; 0.5 mg in 2 ml saline; nebulizer; 30 min P: Saline; 2 ml; nebulizer; 30 min	Treadmill; 6; 90±4% NR; NR 4; 1 24 hr BD x12 hr; SCG x 24 hr; theophylline x 1 wk	≥20% Primary: max % fall FEV_1 Secondary: % protection; complete protection %; clinical protection FEV_1 measured 0, 5, 10, 15, 20, 25, 30 min or until FEV_1 started to increase No AE for any treatments
Borut[80] 1977 U.S. Clinic	Journal article Foundation and Boehringer Ingelheim Crossover	20 20 0	IB; 0.04 mg; MDI; 45 min IB; 0.08 mg; MDI; 45 min P: NA; MDI; 45 min	Bicycle ergometer; 6-8; workload that caused the requisite degree of bronchoconstriction NR; NR 6 [1 control, 5 test]; 1 1 wk All med x 12 hr	>15% Primary: SGaw Secondary: FEV_1 % change from 0 FEV_1 measured at 10, 20 min Yes
Boulet[81] 1989 Canada Clinic	Journal article Government Crossover	12 11 1	IB; 0.08 mg; MDI with aerochamber; 30 min P; NA; MDI with aerochamber; 30 min	Bicycle ergometer; 6; NR NR; NR 4; 1 ≥48 hr Theophyllines x 24 hr; BD x 8 hr	≥10% Primary: mean % protection Secondary: % protection; clinical protection FEV_1 measured at 1, 1.5, 3, min until FEV_1 started to increase; NR

AE = adverse events; BD = bronchodilators; bpm = beats per minute; C = Celsius; cc = cubic centimeter; d = day(s); DSCG = disodium cromoglycate; ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; g/L = grams per liter; hr = hour(s); HR = heart rate; IB = ipratropium bromide; BD= bronchodilator; IM = intra muscular; L = liter; max = maximum; med = medication; MDI = metered dose inhaler; min = minute(s); mg = milligram; ml = milliliter; NA = not applicable; NR = not reported; OB = oxytropium bromide; P = placebo; PEF = peak expiratory flow; RAW = airway resistance; RH = relative humidity; rpm = revolutions per minute; SCG = sodium cromoglycate; SGaw = specific airways conductance; temp = temperature; Tx = treatment; wk = week(s)

Table 35. Description of trials in the therapy review: Anticholinergic therapy (continued)

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Intervention: drug; dose; delivery device time pre-ECT	ECT: type; duration (min); % predicted HR Temp; RH; Study days; challenges/day [N]; Time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Bundgaard[82] 1980 Denmark Clinic	Journal article NR Crossover	18 18 0	IB: 0.5 mg + 2 ml isotonic saline; nebulizer; 30-45 min P: saline; 4 ml; nebulizer; 30-45 min	Free running test; 6; 160 bpm after 2 min running NR; NR 6 [1 no-Tx, 5 test]; 1 24 hr All med x 24 hr	NR Primary: max % fall PEF Secondary: NR PEF measured at 0, 2, 4, 6, 8, 13, 18 min No AE on IB
Chan-Yeung[83] 1977 Canada Clinic	Journal article Drugs supplied by Boehringer Ingelheim Crossover	9 9 0	IB: 0.08 mg; freon-propelled inhaler; 15 min P: lactose powder; NR; spinhaler; 15 min	Treadmill (n=6), jogging outside (n=3); 2.5-6; NR NR; NR 3; 1 3-7 d at same time of d All except oral prednisone x 6 hr	≥15% Primary: Max % fall FEV_1 Secondary: % protection; Complete protection; Clinical protection FEV_1 measured at 5, 10, 15, 20, 25, 30 min NR
Chen[84] 1981 U.S. NR	Journal article Government Crossover	6 6 0	a) atropine plus 1ml IM saline; individual dosing to achieve max bronchodilation; nebulizer; 60 min b) atropine plus 1ml IM saline; double dose of a; nebulizer; 60 min P: distilled water plus 1ml IM saline; 1 ml; nebulizer; 60 min	Treadmill; 10; 180 bpm NR; NR 5; 1 5 ECT in 3 wk at same time of d Theodur, BD, SCG, ICS and prednisone every other d unchanged; testing done on d when prednisone not taken; BD x 4 hr	NR Primary: mean % change FEV_1 Secondary: NR FEV_1 measured at 5-10 min NR
Dorward[85] 1982 United Kingdom Clinic	Journal article NR Crossover	7 7 0	IB: 0.12 mg; nebulizer; 60 min P: saline; 9 g/L; nebulizer; 60 min	Inclined treadmill; 8; 170-180 bpm 20-22°C; 30-50% RH 5; 1 on different d SCG and BD x 24 hr	≥25% Primary: max % fall FEV_1 Secondary: FEV_1 L; mean % fall FEV_1; % protection; complete protection; clinical protection FEV_1 measured at 2, 5, 10, 15, 30 min NR

Table 35. Description of trials in the therapy review: Anticholinergic therapy (continued)

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Intervention: drug; dose; delivery device; time pre-ECT	ECT: type; duration (min); % predicted HR Temp; RH; Study days; challenges/day [N]; Time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Godfrey[86] 1976 United Kingdom Clinic	Journal article NR Crossover	7 7 0	Atropine; 0.2%; nebulizer; 5-10 min P: saline; NA; nebulizer; 5-10 min	Treadmill; 6; 170-180 bpm NR; NR 1; 2 2 hr All med x 12 hr	≥10% Primary: mean % fall PEF Secondary: complete protection; clinical protection PEF measured 2, 4, 6, 8 until 20 min NR
Hartley[87] 1980 United Kingdom Clinic	Journal article Drugs supplied by Boehringer Ingelheim Crossover	10 10 0	a) IB: 0.1 mg; nebulizer; 90 min b) IB:1.0 mg; nebulizer; 90 min P: saline; NA; nebulizer; 90 min	Bicycle ergometer; 8; 80% 20-24°C; not controlled 3; 2 2-3 hr ICS allowed; SCG x 24 hr; BD x 12 hr	≥15% Primary: max % fall FEV_1; max % fall PEF Secondary: FEV_1 L; PEF L/min; % protection; complete protection; clinical protection FEV_1/PEF measured at 1, 5, 10, 15, 20, 25, 30 min No AE during study
Larsson[88] 1982 Sweden Clinic	Journal article Boehringer Ingelheim Crossover	8 8 0	OB; 0.1 mg; MDI; 60 min IB: 0.04 mg; MDI; 60 min P: NA; MDI; 10 min	Bicycle ergometer; 6-9; load increased every min until exhaustion NR; NR 4; 1 24 hr All med x 12 hr	>15% Primary: FEV_1 Secondary: max% fall FEV_1; complete protection FEV_1 measured at 2, 4, 6, 10, 15, 20 min No AE occurred
Neijens[89] 1981 Netherlands Clinic	Journal article Foundation; Drugs supplied by Boehringer Ingelheim Crossover	13 13 0	OB: 0.02 mg; MDI; 20 min P: NA; MDI; 20 min	Treadmill; 6; 175 bpm 22°C; 70% RH 4 consecutive d; 2 2 hr All med x 3 d	≥15% Primary: mean % fall FEV_1 Secondary: max% fall FEV_1; % protection FEV_1 measured at 5, 10, 15, 20 min NR
Poppius[90] 1986 Finland Clinic	Journal article Drugs supplied by Boehringer Ingelheim; Sigrid Juselius Foundation Crossover	10 10 0	a) IB: 0.2 mg; powder capsule; 60 min b) IB 1 mg; powder capsule; 60 min c) IB: 2 mg; powder capsule; 60 min P: Powder capsule; NA; 60 min	Treadmill; 8; workload chosen to induce slight bronchoconstriction Cold air -9±7°C; water content 1.5 mg/L 4; 1 1 to 3 d All antiasthmatic meds during the trial	Not clear Primary: mean % fall FEV_1 Secondary: mean % fall FEV_1 FEV_1 measured at 8, 30 min Yes

Table 35. Description of trials in the therapy review: Anticholinergic therapy (continued)

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Intervention: drug; dose; delivery device; time pre-ECT	ECT: type; duration (min); % predicted HR Temp; RH; Study days; challenges/day [N]; Time between challenges Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
Tashkin[91] 1977 U.S. Clinic	Journal article NR Crossover	15 15 0	Atropine: 1 mg; nebulizer; 10 min P: saline; 0.25 cc; nebulizer; 10 min	Bicycle ergometer; 6-8; 25-watt workload at 60 rpm NR; NR 7 [2 screen, 5 test]; 1 ≤1 wk at same time of d DSCG x 2 wk; oral/inhaled BD x 12 hr	>15% Primary: mean % change in FEV_1 Secondary: NR FEV_1 measured at 0, 5, 15, 20 min NR
Taytard[92] 1987 France Clinic	Journal article NR Crossover	10 10 0	OB: 0.3 mg; MDI; 25 min P: NA; MDI; 25 min	Treadmill; ≤8; 80% NR; NR 2; 1 48 hr Oral/inhaled BD 48 and 12 hr	≥20% Primary: RAW Secondary: complete protection FEV_1 measured at 2, 5, 10, 15, 20 min NR
Thomson[93] 1978 United Kingdom Clinic	Journal article Fison's LtdIndustry Crossover	13 13 0	IB: 2 mg; nebulizer; 20 min P: saline; 9 g/L; nebulizer; 20 min	Treadmill; 5-8; ≥170-180 bpm NR; NR 4; 1 4 ECT within 10 d SCG and BD x 24 hr	≥20% Primary: max % fall FEV_1 Secondary: FEV_1 L FEV_1 measured at 2, 5, 10, 15, 20 min No AE during study
Tullett[94] 1982 United Kingdom Clinic	Journal article NR Crossover	12 8 0	IB 0.12 mg; nebulizer; 30 min P: saline; 9 g/L; nebulizer; 30 min	Treadmill; 8; 160 bpm 20-22°C; 20-40% RH 4; 1 2-3 d SCG and BD x 24 hr	NR Primary: max % fall FEV_1 Secondary: FEV_1 L; % protection; complete protection; clinical protection FEV_1 measured at 2, 5, 10, 15, 30 min Yes
Wolkove[95] 1981 Canada Clinic	Journal article Sigrid Juselius Foundation; Drugs from Boehringer Ingelheim Crossover	8 8 0	IB: 0.04 mg; MDI; 60 min P: 2 puffs; MDI; 60 min	Bicycle ergometer; 8; 300, 600, or 900 km/min indoors 23.3±0.4°C, cold air -9.8±0.6°C; indoors=35±4%; outdoors=65±7% 4; 1 NR All med x 12 hr	≥15% Primary: FEV_1 mean change; effect of temp Secondary: mean % fall FEV_1: mean fall FEV_1 from 0 FEV_1 measured at 5, 10, 20, 30 min No AE
Yeung[96] 1980 Canada Clinic	Journal article Foundation Cross-over	17 17 0	IB: 0.04 mg; MDI; 45 min P: NA; MDI; 45 min	Treadmill; effort to cause a 25% fall in FEV_1 pre-study; 170-180 bpm NR; NR 3; 1 1 to 2 d All med x 12 hrs	≥10% Primary: max % fall FEV_1 / PEF Secondary: mean % fall FEV_1: complete protection; change in % predicted FEV_1 / PEF measured at 3, 9, 15 min Yes

Table 36. Baseline characteristics of patients in trials in the therapy review: Anticholinergic therapy

Author Year	Age (mean±SD) Males: N (%)	Asthma status	Pulmonary function: baseline FEV_1 % predicted (mean±SD)	Max % fall FEV_1 (mean±SD)	Smoking status: N (%)	Atopic status: N (%)	ICS history: N (%)
Boner[79] 1987	11.7±1.4 10/15 (66.7)	Stable	>80	Placebo ECT 40.9±17.2	NR	15/15 (100)	None
Borut[80] 1977	13.1±2.15 18/20 (90)	Stable mild-moderate	77.9±16.01	Control ECT 20-25	NR	20/20 (100)	NR
Boulet[81] 1989	30±10.9 4/11 (57.1)	Stable	90.5±13.1	NR	NR	9/11 (81.8)	4/11 (36.4)
Bundgaard[82] 1980	30.5±7.6 7/18 (38.9)	Stable	NR	Placebo ECT 33.5	Never 10/18 (56); current 3/18 (17) <5/d	17/18 (94.4)	NR (none on oral corticosteroids)
Chan-Yeung[83] 1977	33.1±13.8 5/9 (55.6)	Stable	90.2±12.2	Control ECT 36±15	All non-smokers	4/9 (44.4)	2/9 (22.2)
Chen[84] 1981	13.5±1.76 5/6 (83.3)	Stable	85±10	Placebo ECT 28±14.69	NR	NR	6/6 (100) (testing done on days where no ICS taken)
Dorward[85] 1982	24±9.5 2/7 (28.6)	Stable	2.8±0.87 L	Control ECT 47±18.4	All non-smokers	7/7 (100)	None
Godfrey[86] 1976	8.7±2.9 13/15 (86.7)	Stable	70.3±15.1	Placebo ECT 45.2±15.5	NR	NR	NR
Hartley[87] 1980	32; range 21-48 4/12 (40)	Stable	77.6 (53-113)	Placebo ECT 29.2±12.3	NR	8/10 (80)	3/10 (30)
Larsson[88] 1982	44.8±10.5 5/8 (62.5)	Stable	78.61±27.32	All ≥15	NR	4/8 (50)	2/8 (25)
Neijens[89] 1981	12.5±3.13 9/13 (69.2)	Stable mild-moderate	≥60	Control ECT 32.4±10.8	NR	NR	None
Poppius[90] 1986	27.7±7.21 5/10 (50)	Mild	94.6±15.6	Placebo ECT 14	All non-smokers	5/10 (50)	None
Tashkin[91] 1977	11.7±1.7 14/15 (93.3)	Stable (mild airway obstruction)	79±11	Placebo ECT 18-28	NR	15/15 (100)	None

ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; L = liters; NR = not reported; SD = standard deviation

Table 36. Baseline characteristics of patients in trials in the therapy review: Anticholinergic therapy (continued)

Author Year	Age (mean±SD) Males: N (%)	Asthma status	Pulmonary function: baseline FEV_1 % predicted (mean±SD)	Max % fall FEV_1 (mean±SD)	Smoking status: N (%)	Atopic status: N (%)	ICS history: N (%)
Taytard[92] 1987	19±4 4/10 (40)	Stable	88±16	NR	None or <5 cigarettes/d	NR	None for 1 mo
Thomson[93] 1978	17-3 7/13 (53.8)	Stable	87±22.3	Control ECT 38.1±15.2	All non-smokers	13/13 (100)	None
Tullett[94] 1982	31.2±11.3 5/8 (62.5)	Stable	3.43±0.54 L	Placebo ECT 38.1±14.1	All non-smokers	12/12 (100)	None
Wolkove[95] 1981	28.7±5.4 4/8 (50)	Stable	62.0±16.4 to 69.8±16.7	All ≥15	NR	NR	NR
Yeung[96] 1980	13; range 9-18 14/27 (51.9)	Stable	77.1±21.85	Placebo ECT 35.8±18.1	NR	NR	Mixed

Table 37. Quality assessment of trials in the therapy review: Anticholinergic therapy

Author Year	Described as randomized?	Described as double-blind?	Description of withdrawals/ dropouts?	Method of randomization described and appropriate?	Method of double-blinding described and appropriate?	Method of randomization described but inappropriate?	Method of double-blinding described but inappropriate?	Overall Score: Jadad	Concealment of allocation
Boner[79] 1987	Yes	Yes	Yes	No	No	No	No	3	Unclear
Borut[80] 1977	Yes	Yes	Yes	No	No	No	No	3	Unclear
Boulet[81] 1989	Yes	Yes	Yes	No	No	No	No	3	Unclear
Bundgaard[82] 1980	Yes	Yes	Yes	No	No	No	No	3	Unclear
Chan-Yeung[83] 1977	Yes	No	Yes	No	No	No	No	2	Unclear
Chen[84] 1981	Yes	No	Yes	No	No	No	No	2	Unclear
Dorward[85] 1982	Yes	No	Yes	No	No	No	No	2	Unclear
Godfrey[86] 1976	Yes	No	Yes	No	No	No	No	2	Unclear
Hartley[87] 1980	Yes	No	Yes	No	No	No	No	2	Unclear
Larsson[88] 1982	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Neijens[89] 1981	Yes	Yes	Yes	No	No	No	No	3	Unclear
Poppius[90] 1986	Yes	Yes	Yes	No	No	No	Yes	2	Unclear
Tashkin[91] 1977	Yes	Yes	Yes	No	No	No	No	3	Unclear
Taytard[92] 1987	Yes	Yes	Yes	No	No	No	No	3	Unclear
Thomson[93] 1978	Yes	Yes	Yes	No	No	No	No	3	Unclear
Tullett[94] 1982	Yes	No	Yes	No	No	No	No	2	Unclear
Wolkove[95] 1981	Yes	Yes	No	No	No	No	No	2	Unclear
Yeung[96] 1980	Yes	No	Yes	No	No	No	No	2	Unclear

Key Question T–6: Refractory Period (10 to 15 Minute Warmup and/or Cooldown)

Description of Included Studies

Seven trials[97-103] met the inclusion criteria for the review investigating whether a defined exercise warmup protocol induces a refractory period that attenuates or prevents the EIB/EIA phenomenon within 2 hours of a subsequent ECT. Six trials used a crossover design;[97,99-103] for one abstract the specific design could not be determined.[98] The studies were published between 1979 and 2007. Four trials were conducted in Europe,[97,98,101,102] two in Australia[101,103] and two in North America.[99,100] The definition of EIB/EIA was measured by at least a 10[98,100,101] or 15[97,99,102] percent fall in FEV_1.

In three trials[97,98,102] it was not clear if the ECT following the warmup met the ATS criterion of a work rate equal to 80 to 90 percent of an individually calculated maximum.[164] The time between warmup and ECT ranged from 1 to 49 minutes. The characteristics of the trials are summarized in Table 38.

The baseline characteristics of the participants are presented in Table 39. The number of patients enrolled ranged from 6 to 46. One study[97] included children only, three included adults only,[99,100,102] and three included both children and adults.[98,101,103] All participants in these trials except for one[98] had confirmed asthma; for most, their asthma was mild and stable.

Five of the seven studies investigated two or more warmup protocols. In order to capture all comparisons the protocols were categorized into three subgroups based on the intensity of the routine. Four routines involved several short sprints and are designated "interval" warmups;[97,99,100,103] two studies involved two standardized challenges 45 minutes apart and are designated "continuous high intensity" warmups;[102,103] three involved treadmill runs at work rates of 60 percent and are designated as "continuous low intensity" warmups.[99,101,102] Study arms that involved drug therapy with or without a warmup are not included in this analysis.[100] Finally, the study by Eck et al.,[98] and one arm of the study by Schnall et al.[103] that used a continuous routine followed by an interval routine are reported separately.

Methodological Quality of Included Studies

Table 40 summarizes the methodological quality of the included studies. Overall the seven trials received low Jadad scores ranging from 1 to 2. No study described the randomization method. None stated that the assessors were blind; it was not possible to blind the participants to the type of warmup. Concealment of allocation was unclear in all the trials. The body of evidence is classified as "low."

Quantitative Results

In all studies the mean maximum percent fall in FEV_1 or PEF was measured after a control ECT of 5 to 10 minutes and compared with the percent fall in an identical challenge after a designated warmup routine. The pooled results are presented as a MD in the maximum percent fall in FEV_1 or PEF between the two challenges. Because studies are included in more than one group, only subgroup pooled estimates were calculated.

Interval protocol. Four trials compared an interval warmup to a control challenge with no warmup.[97,99,100,103] The protocols involved repetitive sprints of 26 to 30 seconds at 100 percent maximal oxygen consumption (VO_{2max}) or higher. The mean difference in the maximum percent

fall in FEV_1 ranged from an improvement of 4.8 to 16.1 percent over the control challenge. The pooled results showed that a series of short intense sprints attenuated the EIB/EIA response by a mean of 10.6 percent (95 percent CI: -14.7, -6.5; I^2=15 percent) (Figure 27). One study reported that one of the 12 participants had falls in FEV_1 of less than 15 percent[99] and would be classified as having obtained complete protection from EIB/EIA following the interval warmup.

Continuous low intensity protocol. Three trials compared a continuous low intensity warmup that ranged from 3 minutes[101] to 30 minutes[102] to a control challenge with no warmup. Exercise intensity for the warmup was 60 percent of maximum heart rate,[101] 60 percent of VO_{2max},[99] and reported as low intensity in the third study.[102] The mean difference in the maximum percent fall in FEV_1 ranged from no improvement to 20.6 percent over the control challenge. The pooled results showed that this type of warmup attenuated the EIB/EIA response by a mean of 12.6 percent (95 percent CI: -26.7, 1.5; I^2=90 percent) (Figure 27). One study also reported that 6 of the 12 participants had falls in FEV_1 of less than 15 percent and classified them as having obtained complete protection from EIB.[99]

Continuous high intensity protocol. Two trials compared a continuous high intensity warmup[102,103] to a control challenge with no warmup. Exercise intensity for the warmup was a heart rate equal to180 beats per minute[103] and 98±2 percent of predicted maximum.[102] The mean difference in the maximum percent fall in FEV_1 ranged from very little improvement (0.99) to 17.6 percent over the control challenge. The pooled results showed that this type of warmup attenuated the EIB/EIA response by a mean of 9.8 percent (95 percent CI: -26.0, 6.4) (Figure 27). Substantial heterogeneity was identified (I^2=89 percent).

Combination protocols. Eck et al.[98] reported that there was no significant difference among the three protocols they investigated—one each of continuous 10 minutes of low intensity running, 10 minutes of running in intervals, and 10 minutes of exercising with increasing intensity. No data on the intensity of each warmup were reported. When combined, the three protected 79 percent (36/46) of participants from EIB/EIA (cutpoint not reported). The combined mean maximum percent fall in FEV_1 on the challenge following all warmup protocols was compared with no warmup and indicated a mean improvement of 11.0 percent (95 percent CI: 7.5, 14.6) (Figure 27).

One of three protocols in the Schnall and Landau[103] trial involved a combination of continuous and interval segments—a 6 minute treadmill run (heart rate 180 beats per minute), a 10 minute rest followed by 7 x 30 second sprints (treadmill speed increased 120 to 130 percent over first run), then a 20 minute rest before the final challenge of the same intensity as the original 6 minute run. The mean difference in the maximum percent fall in FEV_1 compared with no warmup was 10.4 percent (95 percent CI: 0.2, 21.1).

Other comparisons: One study reported no significant changes among three formats of warmup in measures of respiratory heat and water loss.[99]

Figure 27. Warmup vs. no warmup in pre-exercise treatment of EIB/EIA: maximum percent decrease in FEV_1 or peak expiratory flow

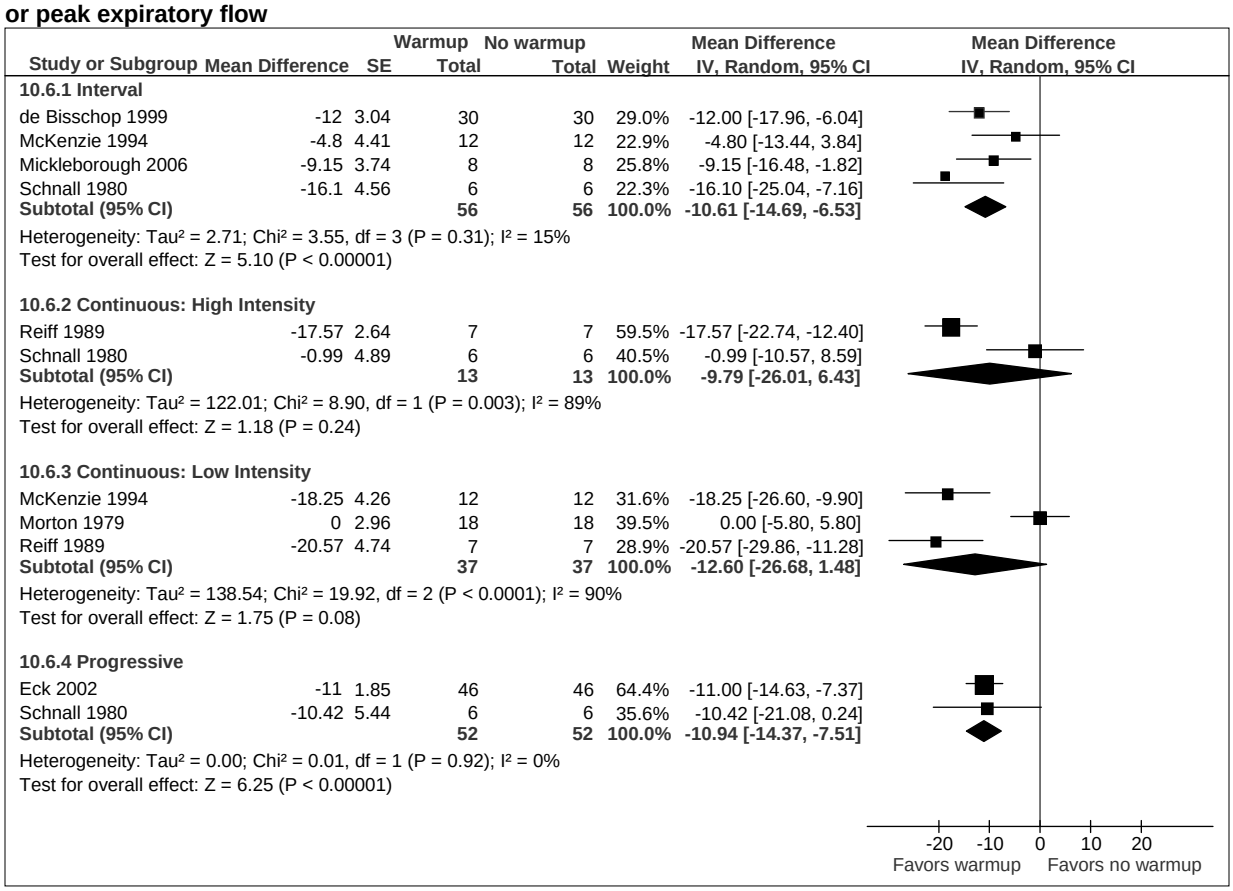


Table 38. Description of trials in the therapy review: Refractory period

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Warmup protocol Description; Rest	ECT type/duration (min) following no warmup or warmup	ECT: temp; RH Number of protocols; protocols per day [N]; time between protocols Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
de Bisschop[97] 1999 France Treatment center	Journal article NR Crossover	30 30 0	No warmup or Protocol 1: interval: 2 sets of 5 x 26 sec sprints, 1.5 min between, 5 min between sets (7.5% of the distance and 120% of the speed of FRAST) 10 min rest	FRAST: running as fast as possible x 7 min (mean distance =1,171±142 m)	4±5°C; 1.5±0.5 mmHg 2; 1; 24 hr, at mid-day SABA x 12 hr	≥15% Primary: mean % fall PEF Secondary: PEF L/min; mean % fall PEF predicted; PEF measured at post each sprint, 5, 10 min post sets, 5, 10 min post-FRAST NR
Eck[98] 2002 Germany, Switzerland Clinic	Abstract NR Not clear	46 NR NR	No warmup or 5 min stretching, no rest, plus Protocol 1: continuous: 10 min steady training Protocol 2: interval: 10 min interval running Protocol 3: progressive: 10 min exercises with increasing intensity	Treadmill x 10 min steady running	NR; NR 4; not clear; not clear NR	≥10% Primary: mean % fall FEV_1 Secondary: complete protection NR

AE = adverse events; AUC = area under the curve; bpm = beats per minute; C = Celsius; ECT = exercise challenge test; EIB/EIA = exercise-induced bronchoconstriction/asthma; FEV_1 = forced expiratory volume in 1 second; FRAST = free running asthma screening test; hr = hour(s); HR = heart rate; ICS = inhaled corticosteroid; km/h = kilometers per hour; L = liter; max = maximum; µg = microgram; min = minute(s); mmHg = millimeter of mercury; NR = not reported; PEF = peak expiratory flow; RH = relative humidity; SABA = short-acting beta-agonist; Sal = salbutamol; SCG = sodium cromoglycate; sec = second(s); temp = temperature; $V0_2$ = oxygen consumption; wk = week(s)

Table 38. Description of trials in the therapy review: Refractory period (continued)

Author, Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Warmup Protocol Description; Rest	ECT type/duration (min) following no warmup or warmup	ECT: temp; RH Number of protocols; protocols per day [N]; Time between protocols Withheld asthma med; class; time	Definition EIB/EIA (% fall FEV_1) Outcomes: Primary Secondary Adverse events
McKenzie[99] 1994 Canada Volunteers	Journal article NR Crossover	12 12 0	No warmup or Protocol 1: continuous low intensity: treadmill x 15 min at 60% VO_{2max}; 2 min rest; Protocol 2: interval: 8 x 30 sec sprints at 100% VO_{2max} separated by 1.5 min rest; 2 min rest	Treadmill x 6 min at 90% VO_{2max}	20.7±1.2°C; ambient room humidity 3; not clear (3 sessions); not clear Caffeine and exercise x 4 hr.	≥15% Primary: max % decrease FEV_1 Secondary: complete protection FEV_1 measured at 0.5 min, then every 2 min to 25 min; NR
Mickleborough[100] 2007 U.S., United Kingdom University and local community	Journal article NR Crossover	8 8 0	No warmup or Protocol 1: Interval: 8 x 30 sec sprints with 45 sec recovery between; 15 min rest (interval intensity equal to VO_{2max}) Protocol 2: Sal 200 µg plus 8 x 30 sec sprints with 45 sec recovery between sprints; 15 min rest; Protocol 3: Sal 200 µg; 15 min rest	Treadmill x 8 min at 85-90% predicted max HR; wore a noseclip	23°C; 50% 4; 1; ≥96 hr SABA x 12 hr, caffeine/alcohol x 8 hr, exercise x 24 hr	≥10% Primary: max % decrease FEV_1; AUC Secondary: NR FEV_1 times measured at 1, 5, 10, 15 min NR
Morton[101] 1979 Australia Local volunteer	Journal article Foundation Crossover	19 18 1	No warmup or Protocol 1: continuous low intensity: treadmill x 3 min at 60% predicted max HR; 1 min rest;	Treadmill x 5 min at 85% predicted max HR	Room temp; NR 2; 1; ≥8 day All med and exercise x 12 hr	≥15% Primary: max % decrease FEV_1 Secondary: FVC % change FEV_1 times measured at 5, 10, 15, 20, 30 min 1 AE

Table 38. Description of trials in the therapy review: Refractory period (continued)

Author Year Country Source	Publication status Funding Trial design	Randomized [R] Analyzed [A] Withdrawals [W]	Warmup Protocol Description; Rest	ECT type/duration (min) following no warmup or warmup	ECT: temp; RH Number of protocols; protocols per day [N]; Time between protocols Withheld asthma med; class; time	Definition EIB/EIA Outcomes: Primary Secondary Adverse events
Reiff[102] 1989 United Kingdom Clinic Volunteers	Journal article NR Crossover	7 7 0	Protocol 1: continuous high intensity: treadmill at 15% incline; 6 km/h x 6 min; 45 min rest HR=98±2% predicted max Protocol 2: continuous low intensity: treadmill at 3% incline, 6 km/h x 30 min; 21 min rest HR=88±32% predicted max	Treadmill x 6 min at 15% incline; 6 km/h; HR=97±3% predicted max	19.9±0.7°C; 39-50±4.0% 2; 1; 2 sessions within 1 wk at same time of d ICS x 24 hr; SABA x 8 hr	≥15% Primary: max % decrease FEV_1 and PEF Secondary: Mean % fall FEV_1 and PEF; AUC FEV_1/PEF measured at every 5 min to 90 min NR
Schnall[103] 1980 Australia NR	Journal article Government Crossover	6 6 0	Protocol 1: continuous high intensity: Treadmill x 6 min at 10% incline (HR 180 bpm), 49 min rest Protocol 2: Progressive: Treadmill x 6 min at 10% incline (HR 180 bpm); 10 min rest; 7 x 30 sec sprints with 2.5 min between (speed 120-130% of 1st run); 20 min rest Protocol 3: Interval: 7 x 30 sec sprints with 2.5 min between (speed 120-130% of 1st run) 20 min rest	Treadmill x 6 min at 10% incline; HR 180 bpm	21-23.5±1.2°C; 0.55 3; 1; 3 sessions in 4 wk SABA and SCG x 8 hr	NR Primary: max % decrease FEV_1 and PEF Secondary: FEV_1 L; PEF L/min FEV_1 / PEF measured at 0, 2, 5, 10, 15, 25 up to 80 min Yes

Table 39. Baseline characteristics of patients in trials in the therapy review: Refractory period

Author Year	Age (mean±SD) Males: N (%)	Asthma status	Pulmonary function: baseline FEV_1 % predicted (mean±SD)	Max % fall FEV_1 (mean±SD)	Smoking status: N (%)	Atopic status: N (%)	ICS history: N (%)
de Bisschop[97] 1999	12; range 8-15 21/30 (70)	Stable, mixed severity	PEF: 99±15%	PEF: 37±14.5	NR	NR	≥8/30 (26.7)
Eck[98] 2002	Range 6-19 NR	NR	NR	NR	NR	NR	NR
McKenzie[99] 1994	26.5±7.8 3/12 (33.3)	Stable	3.42±1.05 L	>30	Non-smokers	NR	None
Mickleborough[100] 2007	19.5±1.2 NR	Mild-persistent	92.4±6.12 (3.5±0.82 L)	18.25±4.01	Never smoked	NR	8/8 (100)
Morton[101] 1979	19.7; range 11-33 10/18 (55.6%)	Stable	100	38.1	NR	NR	NR
Reiff[102] 1989	25.4±6.6 5/7 (71.4)	Stable, mild-persistent	80.6±20.7	FEV_1: 46±6.9; PEF: 51±10.6	NR	7/7 (100)	2/7 (28.6)
Schnall[103] 1980	Range 12-31 4/6 (66.7)	Stable	84.1 (2.7±0.71 L)	22.8±8.08	NR	NR	None

FEV_1 = forced expiratory volume in 1 second; L = liters; NR = not reported; PEF = peak expiratory flow; SD = standard deviation

Table 40. Quality assessment of trials in the therapy review: Refractory period

Author Year	Described as randomized?	Described as double-blind?	Description of withdrawals/ dropouts?	Method of randomization described and appropriate?	Method of double-blinding described and appropriate?	Method of randomization described but inappropriate?	Method of double-blinding described but inappropriate?	Overall Score: Jadad	Concealment of allocation
de Bisschop[97] 1999	Yes	No	Yes	No	No	No	No	2	Unclear
Eck[98] 2002	Yes	No	No	No	No	No	No	1	Unclear
McKenzie[99] 1994	No	No	Yes	No	No	No	No	1	Unclear
Mickleborough[100] 2007	Yes	No	Yes	No	No	No	No	2	Unclear
Morton[101] 1979	Yes	No	Yes	No	No	No	No	2	Unclear
Reiff[102] 1989	Yes	No	Yes	No	No	No	No	2	Unclear
Schnall[103] 1980	Yes	No	Yes	No	No	No	No	2	Unclear

Chapter 4. Discussion

Diagnostic Test Accuracy Review

A valid test to determine if EIB or EIA is present must involve a standardized measure of effort (heart rate or ventilation rate) or dose of inhalant and be of sufficient duration to produce a response in susceptible subjects. Airway response measures must also be standardized. Testing protocols for airway constriction can be classified into direct or indirect tests. Indirect challenges such as exercise, eucapnic voluntary hyperpnea (EVH), and inhaled mannitol are thought to cause inflammatory cells to release mediators such as leukotrienes, prostaglandin, and histamine which provoke smooth muscle constriction.[20] In contrast, direct tests such as methacholine or histamine act directly on smooth muscle receptors to cause constriction independent of airway inflammation.[19]

Using a comprehensive search strategy and concerted efforts to avoid publication and selection bias, this review identified all the available evidence to assess the diagnostic test characteristics of six tests for the diagnosis of EIB/EIA. In total, we identified 27 studies that met our inclusion criteria. The number of studies available to address each of the six key questions ranged from 2 to 16.

There are many methodological considerations when undertaking a systematic review of the diagnostic literature. To determine the accuracy of a diagnostic test, a reference standard must be available for comparison. The reference test used for this report was the exercise challenge test (ECT) as detailed by the ATS.[18] The guidelines cover water content and temperature of the inspired air plus work effort required for either treadmill or bicycle ergometer testing. According to the ATS criteria,[18] during the ECT participants should inspire dry air at a temperature of less than 25°C with a noseclip in place to force mouth breathing. Nasal breathing decreases the water loss from the airways. Temperature and relative humidity (RH) during testing should be documented, and RH should be low (50 percent or less). It is unclear if the ambient humidity in the typical air conditioned laboratory (30 to 50 percent water vapor saturation) is less likely to induce airway narrowing as compared with perfectly dry air obtained from compressed gas (i.e., RH ~0 percent).[18] However, as airway drying is the primary trigger for EIB/EIA,[19] it would seem logical that tests completed with compressed air would be more sensitive for detecting EIB/EIA. In this review, many studies had the participants inspire room air as detailed in ATS guidelines, while others used compressed air during their ECT.

Among the included studies, detailed reporting of the ECT protocol varied, and in several cases it was not clear if the challenge met ATS recommendations particularly when it came to nose versus mouth breathing, effort required, and duration. Treadmill grade and speed must be individually chosen and progressively increased in the first minutes to produce 6 to 8 minutes of near maximum target heart rates (i.e., 80 to 90 percent of the predicted rate for age). Ventilation should reach 40 to 60 percent of the predicted maximum voluntary ventilation. In a bicycle ergometer challenge a target work rate is determined to achieve target ventilation and the work rate is gradually increased until the target exercise intensity is maintained for 4 to 6 minutes. With either method, the subject must reach the target heart or ventilation rate in the first 4 minutes as water loss and airway drying determine the development of EIB/EIA.[18] Since the specifics of the ECTs were not consistently reported in full, some exercise challenges may not have met these standards. Furthermore, a number of studies used higher diagnostic cutpoints of a 15 or 20 percent fall in FEV_1 post-exercise instead of the ATS guideline of a 10 percent drop.

We could not always extract results for the 10 percent cutpoint. We suspect that the variability in methodology used for the reference standard ECT may be the cause of some heterogeneity in comparisons with other EIB/EIA diagnostic methods.

A key concern, which may also have contributed to the heterogeneity observed across all the diagnostic comparisons, was that of a spectrum bias. Ideally, studies should have a sample of participants who are representative of the population being examined for EIB/EIA. That is, studies should have participants that span the range from high to low likelihood of EIB/EIA so that the true positive and true negative numbers are approximately the same. Many studies included in these reviews purposely recruited participants who either had or did not have a history of EIB/EIA or asthma (asthma increases the likelihood of having EIA) or they did not mention clinical history or provide baseline data. Cumulatively, only 6 percent of studies had a representative sample and only 21 percent stated their inclusion criteria. Virtually all studies recruited volunteers who were willing to undergo the tests being compared. The lack of a representative patient spectrum limits the generalizability of the results to the target population of people with suspected EIB/EIA and therefore a pooled estimate of sensitivity and specificity is not reliable.

Table 41 and the following sections review the individual tests examined in the review.

Self-report. Since many patients present to clinicians with simply their story of breathing difficulties following exercise, the first question in this diagnostic review examined the accuracy of self-reported history or symptoms. EIB/EIA may be associated with symptoms such as shortness of breath, cough, wheeze and chest pain,[18] and therefore these symptoms may lead clinicians to suspect EIB/EIA. For clinicians and patients, the diagnostic test characteristics of self-report are important to understand.

Despite extensive searching, only two studies addressed this question. While the results of one of the studies[21] comparing post-exercise cough to an ECT are encouraging (89 percent sensitivity, 86 percent specificity), this is not sufficient evidence to conclude that self-report of symptoms is a reliable diagnostic tool for EIB/EIA (Table 41). There were too few studies to produce reliable ROC curves. Furthermore, given the complexity and variability of respiratory symptoms, recent research in chronic asthma has shown that objective lung testing is vital for a valid diagnosis[165] and there is no reason not to apply this to a diagnosis of EIB/EIA.

Quality of evidence. The evidence from this group of two studies was graded as “very low”. Both study designs were rated low and there are serious limitations due to the lack of a representative spectrum of participants and uncertainty whether the ECTs met the ATS guideline recommendations.[18] The diagnostic thresholds differed and the sensitivity estimates are inconsistent and imprecise.

Methacholine (MCH) challenge. MCH is considered a direct challenge as it acts on smooth muscle acetylcholine receptors, causing contraction and airway narrowing.[23] It has been noted that airway responsiveness to pharmacologic agents such as MCH differs from hyper-responsiveness in response to physical stimuli such as exercise and osmotic agents.[18]

The review identified 16 studies that met the inclusion criteria for the diagnostic test accuracy review of the MCH challenge. Overall, the study quality varied, and there was a concern of spectrum bias in all but one study.[23] Regardless of the threshold level for MCH (8 mg/ml or 16 mg/ml), there was considerable heterogeneity across individual study estimates for sensitivity (66 to 100 percent at 8 mg/ml; 0 to 100 percent at 16 mg/ml) and specificity 0 to 100 percent at either threshold. (Table 41) Moreover, the area under the curve (AUC) of the ROC was marginally more than 0.5 for any of the FEV_1 cutpoints (10, 15, or 20 percent) or MCH

thresholds. Based on these results we cannot conclude that the MCH challenge is a valid test to diagnose EIB/EIA.

Unlike exercise challenges, a positive airway response to MCH does not infer the presence of inflammatory cells or their mediators;[20] therefore, it is not surprising that MCH shows variable sensitivity and specificity to detect EIB/EIA. It has been suggested[18] that a positive MCH test should not be used to infer EIB/EIA and likewise, a negative MCH should not be used to exclude EIB/EIA.

Quality of evidence. The evidence from this group of 15 studies was graded as "moderate". The study designs were rated high; however, there are serious limitations to the body of evidence as a whole. Only one study had a representative spectrum of participants and blinded the assessors to test results. It is unclear whether eight of the ECTs met the ATS guideline recommendations.[18] The sensitivity estimates are reasonably consistent but are imprecise in the EIA participants. Specificity estimates are inconsistent and imprecise.

Sport or venue specific challenges. Sport or venue specific challenges refer to challenges in the specific sport (e.g., basketball, soccer) or at the venue of activity (e.g., hockey arena, swimming pool). They are advantageous in that the athlete can exercise in the conditions where they become symptomatic and the tests are reasonably inexpensive; however, coordinating the two tests and ensuring good quality control on both can be problematic.

Five studies addressed the key question of sport or venue specific exercise challenges (Table 41). Three studies focused on swim challenges and two assessed cold weather challenges. All studies involved elite athletes. The sensitivity of the field tests ranged from 0 to 100 percent. Specifity also ranged from 0 to 100 percent; however, in one study,[41] all participants had a history of EIB/EIA and therefore had a high pre-test probability of testing positive on both tests. In the studies that did not have this select population, the specificity ranged from 79 to 100 percent. There were too few studies to produce reliable ROC curves. Althought sport specific challenges are one of the recommended challenges for diagnosing EIB/EIA in elite athletes,[34] in total, only seven athletes tested positive in their own field of competition while 16 were positive on a standardized ECT. It is not clear why this occurred, although it is possible that the level of minute ventilation and differences in environmental conditions played a role. Sport specific challenges may be useful in identifying athletes who do *not* have EIB/EIA but additional testing such as a standardized ECT may be required to confirm a diagnosis.

Quality of evidence. The evidence from this group of five studies was graded as "low". The study designs were rated high; however, there are serious limitations to the body of evidence as a whole. No study had a representative spectrum of participants or blinded the assessors to test results. It is unclear whether two of the ECTs met the ATS guideline recommendations.[18] Both the sensitivity and specificity estimates are inconsistent and imprecise.

Eucapnic voluntary hyperpnea (EVH) challenge. EVH challenge is a test based on the premise that the increased minute ventilation with exercise is responsible for airway constriction in susceptible participants.[19] Currently, EVH is the challenge recommended by the International Olympic Committee Medical Commission to identify EIB/EIA among Olympic athletes.[48]

The stimulus for the airways to narrow in response to exercise is the water lost by evaporation from the airway surface and the osmotic and thermal effects arising from this.[18] Theoretically, conditioning large volumes of cold inspired air places a greater burden on the airways to reheat and rehumidify it quickly as compared with inspiring warmer, humid air. Therefore, it is likely that additional (i.e., small) airways would be recruited to achieve the task and this would increase airway dehydration. Similarly, inspiration of cold air during EVH would

increase the likelihood of bronchoconstriction compared with EVH using room temperature air. In the study by Eliasson et al.[42] participants performed EVH tests while inspiring air at room temperature or inspiring air cooled to between minus 18°C and minus 26°C. Despite the increased conditioning of the air required during the cold air trial, there was no difference in post-EVH FEV_1 response between the cold versus room temperature challenges.

It is worth noting that EVH challenges are likely the most technically difficult of all the EIB/EIA diagnostic tests to perform for a variety of reasons. First, minute ventilation must be measured accurately in real-time and displayed so that participants can receive feedback on their target minute ventilation. The substantial increase in minute ventilation with the challenge will cause hypocapnea, which can cause bronchoconstriction[166] as well as nausea and fainting. It is for this reason that EVH trials are performed with participants rebreathing a gas mixture of approximately five percent CO_2 so that arterial CO_2 levels can be maintained at resting eupneic levels. Importantly, rebreathing a gas mixture for 5 to 6 minutes may also cause hypoxemia if the gas mixture does not contain an elevated oxygen concentration. Thus, additional monitoring equipment as well as well-trained respiratory or exercise physiology staff are required to maintain CO_2 and O_2 levels within normal physiological ranges during EVH challenges.

Seven studies met the inclusion criteria to assess the diagnostic accuracy of EVH (Table 41). In general study quality raised questions of bias, in particular, there was a concern of spectrum bias in all studies. Overall, the sensitivity and specificity was heterogeneous with values ranging 25 to 100 percent, and 0 to 74 percent, respectively. It is unclear whether an EVH challenge is identifying the same people that experience a fall in FEV_1 of 10 percent or more on an ECT, particularly in a population of athletes with an unclear history of asthma. The EVH challenge resulted in a higher proportion of false positives (FP) (i.e., negative on the ECT but positive on EVH) among participants with no or unknown history of EIB/EIA. The proportion of FP ranged from 25 to 71 percent. The participants included both elite athletes (n=63) and those with unknown activity levels (n=20). Based on the available evidence, it is unclear if the EVH challenge is more sensitive to EIB/EIA, or if the mechanism that triggers the bronchoconstriction is different from that for the ECT, or if level of minute ventilation achieved on an ECT according to ATS recommendations is less than the level achieved in an EVH challenge particularly in athletes. Among participants with a history of EIB/EIA, the proportion of FPs ranged from 0 to 5 percent in participants with unknown activity levels. Among athletes, the proportion with a FP result was 27 percent. Further research is needed to determine if the EVH challenge would be an appropriate add-on test to a standardized ECT in athletes with symptoms of EIB/EIA. Based on this evidence, it is unclear whether EVH challenge is more accurate diagnostic test for EIB/EIA compared with a standardized ECT.

Quality of evidence. The evidence from this group of seven studies was graded as “low”. The study designs were rated high; however, there are serious limitations to the body of evidence as a whole. No study had a representative spectrum of participants or blinded the assessors to test results. It is unclear whether the ECTs met the ATS guideline recommendations.[18] Furthermore, the sensitivity and specificity estimates are inconsistent and imprecise.

Free running asthma screening test (FRAST). Free running has often been used in screening large groups for EIB/EIA because of the ease in performing such challenges.[19] Three studies met the inclusion criteria for assessing the diagnostic accuracy of the FRAST (Table 41). Participants in all the studies were children (younger than 15 years), and all tests took place indoors. Despite being able to run freely during the FRAST, the reported average heart rate during the challenge for each group was 80 percent or greater of maximum and was comparable

to the ECT. None of the studies had a representative patient spectrum. Sensitivity and specificity were modest (60 to 67 percent and 47 to 67 percent, respectively). There were too few studies to produce reliable ROC curves. While the FRAST is easy to perform, there is insufficient evidence to conclude that it accurately identifies people with EIB/EIA compared to a standardized ECT.

Quality of evidence. The evidence from this group of three studies was graded as "very low". The study designs were rated medium; however, there are serious limitations to the body of evidence as a whole. No study had a representative spectrum of participants or blinded the assessors to test results. It is unclear whether two of the ECTs met the ATS guideline recommendations.[18] The sensitivity and specificity estimates are consistent but imprecise.

Mannitol provocation test. Recently, a mannitol provocation test has been developed to examine airway hyper-responsiveness. Like exercise, mannitol is considered an indirect bronchial provocation test. Mannitol increases osmolarity, which causes the release of endogenous mediators such as prostaglandin, leukotrienes and histamine, and results in smooth muscle contraction.[50,51] Mannitol has the advantage that it can be performed with minimal equipment (i.e., a metered-dose inhaler and spirometer).

Three studies met the inclusion criteria for the diagnostic test accuracy review of mannitol (Table 41). Sensitivity ranged from 58 to 96 percent; specificity ranged 65 to 78 percent. At this time there is insufficient evidence to conclude that the mannitol provocation test is a reliable test to diagnose EIB/EIA.

Quality of evidence. The evidence from this group of 3 studies was graded as "moderate". The study designs were rated high; however, there is reasonable concern regarding the limitations to the body of evidence as a whole. Only one study had a representative spectrum of participants and blinded the assessors to test results. All three of the ECTs met the ATS guideline recommendations.[18] The sensitivity and specificity estimates are reasonably consistent but are imprecise.

Table 41. Summary of sensitivity and specificity for the diagnostic test accuracy review

Index test	# studies, sample size	ECT type (# studies) Definition of EIB/EIA (# studies)	Sensitivity point estimate or range mean % (95% CI)	Specificity point estimate or range mean % (95% CI)	ECT +ve (≥10% fall FEV_1) N (%)	Index test +ve N (%)	Evidence Grade
Self-report	2, N=206	Treadmill (2)					Very low
		≥10% fall FEV_1 (1)	89% (67, 99)	86% (64, 97)	19 (48)	20 (50)	
		≥15% fall FEV_1 (1)	36% (17, 59)	85% (78, 90)	20 (13)	30 (18)	
Methacholine	16, N=1,048	Treadmill (10) Bicycle ergometer (6)	≥10% fall FEV_1				Moderate
		ECT: ≥8% fall FEV_1 (1), ≥10% fall FEV_1 (6), ≥15% fall FEV_1 (2), ≥18% fall FEV_1 (1), ≥20% fall FEV_1 (5)	0-100%; (MCH_{PC20} <8mg/ml)	0-100%	331 (57)	416 (71)	
		MCH: ≥20% fall FEV_1 at various doses MCH	55-100% (MCH_{PC20} <16mg/ml)	0-100%	420 (53)	498 (63)	
Sport specific challenge	5, N=95	Treadmill (3), bicycle ergometer (2)	≥10% fall FEV_1 Swim challenge		11 (19)	5 (9)	Low
		≥10% fall FEV_1 (4) ≥20% fall FEV_1 (1)	0-50%	83-100%			
			Winter sports n=37 100% (48-100) (1 study)	79% (49, 95) (1 study)	5 (14)	26 (70)	
Eucapnic voluntary hyperpnea	7, N=138	Treadmill (4), bicycle ergometer (3)	≥10% fall FEV_1				Low
		ECT: ≥10% fall FEV_1 (4), ≥20% fall FEV_1 (1), NR (2) EVH: ≥10% fall FEV_1 (4), NR (3)	25-90%	0-71%	42 (30)	74 (54)	
FRAST	3, N=99	Treadmill (1), bicycle ergometer (2)					Very low
		≥10% fall FEV_1 (1)	≥10% fall FEV_1: 60-67%	47-67%	13 (38)	18 (53)	
		≥20% fall FEV_1 (2)	≥20% fall FEV_1: 53%	100%	30 (50)	16 (27)	
Mannitol	3, N=423	Treadmill (2), bicycle ergometer (1)	≥10% fall FEV_1				Moderate
		ECT: ≥10% fall FEV_1 (3) Mannitol: ≥15% fall FEV_1 (3)	58-96%	65-78%	202 (48)	203 (48)	

ECT = exercise challenge test; EVH = eucapnic voluntary hyperpnea; FEV_1 = forced expiratory volume in 1 second; FRAST = free running asthma screening test; MCH = methacholine; PC = provocative concentration

Limitations

In addition to the issues identified regarding ECT and index test performance, there are several limitations that need to be discussed regarding systematic reviews of diagnostic test accuracy. First, there is a possibility of publication bias. The impact of publication bias on the results of diagnostic test accuracy reviews is not well understood nor have the tools to investigate publication bias in these reviews been developed.[167] However, we conducted a comprehensive and systematic search of the published literature for potentially relevant studies. Search strategies included combinations of subject headings and free text words. These searches were supplemented by handsearching for gray literature (i.e., unpublished or difficult to find studies). Despite these efforts, we recognize that we may have missed some studies.

Overall, EIB/EIA literature is not indexed well and authors are not consistent in using the terms in titles or abstracts that clearly describe the scope of their research. There are also a variety of activities and sports that can potentially cause EIB/EIA. It is impossible to account for every variation and term within the search strategy. Knowing this, the search strategy was designed to be highly sensitive in order to avoid missing any potentially relevant articles and 18 electronic databases were searched in order to retrieve as many pertinent studies as possible.

There is also a possibility of study selection bias. We employed at least two independent reviewers to identify potentially relevant studies, and feel confident that the studies that were excluded from this report were done so for consistent and appropriate reasons.

A further limitation was that not all studies that seemed potentially relevant were designed as diagnostic test accuracy studies but they did compare two test methods of interest; however, the data presented were not in a useful form to evaluate the diagnostic accuracy of the comparison. In order to be included, a study had to report sufficient data to generate a 2x2 table of the reference standard and index test results based on one or more diagnostic thresholds.

Finally, we did not pool the sensitivity and specificity data in this report. A decision was made that the populations, tests, and study designs were sufficiently heterogeneous for each of the key questions that pooling would be invalid. Where appropriate we wanted to produce AUC results for ROC curves; however, given the small number of studies that addressed each of the key questions, an ROC curve was possible only for MCH versus ECT.

Conclusions

Despite exhaustive efforts to identify evidence regarding the diagnostic test characteristics of tests used to identify patients with EIB/EIA, few studies were identified. Moreover, the studies that were identified suffered from considerable test variability and spectrum bias. In all included studies, the participants were volunteers and varied from exclusively elite athletes with or without documented or suspected EIB/EIA to patients with or without documented or suspected EIB/EIA who were not trained athletes. In the many of studies physical fitness was not addressed at all. The diversity in included populations and the fact that there were not many studies comparing the same diagnostic tests precluded more detailed subgroup analysis of the issue of EIB versus EIA. However, we do not believe these limitations invalidate the results presented in the review as the reviewers analyzed the data as vigorously as it allowed. The results of this report apply to patients being screened for EIB/EIA as well as the clinicians caring for them.

On the basis of this review, there is no clear evidence to support that any of the six index tests studied are equivalent to, or better than, the standardized ECT to diagnose EIB/EIA. At this time none can be recommended to replace the ECT for diagnosing EIB/EIA in the general population. EIB/EIA remains a complex phenomenon that does not always occur in the same individual every time they under go a challenge. Combining history, symptoms, objective testing plus trial and error therapy may still be the preferred path to an active life in those that have EIB/EIA.

Therapy Review

Using a comprehensive search strategy and concerted efforts to avoid publication and selection bias, this review identified all the available evidence to assess the effectiveness of six interventions (five pharmacologic and one nonpharmacologic) to treat EIB/EIA. Overall, we identified 109 studies that met our inclusion criteria. The number of studies available to address each of the six key questions ranged from 4 to 17 involving between 40 and 272 participants.

There are many methodological considerations when undertaking a systematic review of the therapeutic literature. When determining the effectiveness of a therapy, the highest level of evidence arises from well-conducted RCTs. EIB/EIA is a unique condition. It would not exist if not triggered by vigorous exercise and, although the bronchoconstriction can be severe; it generally resolves spontaneously over the course of an hour and leaves no permanent sequelae. The therapeutic drugs used for EIB/EIA are short-acting and are rapidly cleared from the body. As a result, therapy trials for this condition lend themselves to crossover RCT methodology and the majority of trials in these reviews employed this design. The advantage of a crossover compared with a parallel group design is that all participants receive all interventions and, therefore serve as their own control. This reduces sample size requirements. However, concerns with washout periods, carryover effects, and changes over time mean trialists must design the timing and frequency of ECTs with this in mind.

Since asthma is a common chronic condition, in most countries guidelines exist for the treatment of this disease. Not surprisingly, the treatment options for EIB/EIA mirror those for symptoms in chronic asthma—mainly, bronchodilators and anti-inflammatory agents. Like an asthma attack, an EIB/EIA attack can produce symptoms such as shortness of breath, cough, wheeze and chest pain,[143] and, as in asthma, these symptoms are amenable to treatment with bronchodilators. Since many of the anti-inflammatory agents improve asthma control, clinicians and researchers have been curious to know if they also have an effect on EIB/EIA.

The following sections summarize the pharmacologic and nonpharmacologic treatments addressed in this report (Table 42 and Figure 28). The pharmacologic interventions are further divided into bronchodilating and anti-inflammatory agents.

Table 42. Prophylactic therapy for EIA: Pulmonary function results

Comparisons Intervention vs. control	N trials (SS_i vs. SS_c) MD % fall FEV_1/PEF (95% CI)*	Clinical protection ≥50% N trials (SS_i vs. SS_c) RR (95% CI)†	Mean % protection of intervention over control (95% CI)	Complete protection N trials (SS_i vs. SS_c) RR (95% CI)†	Evidence Grade
Leukotriene receptor antagonists vs. placebo	N=9 (267 vs.267) 8.9 (6.9, 11.0)	NR	NR	≤10% fall FEV_1 N=4 (124 vs. 123) 1.87 (0.77, 4.56)	Moderate
Inhaled corticosteroids vs. placebo	N=4 (50 vs. 50) 5.0 0.0, 9.9)	NR	BV 6%; BUD 17%; FP 49%	NR	Moderate
MCS (Nedocromil sodium) vs. placebo	N=17 (240 vs. 240) 15.6 (13.2, 18.2)	NR	51 (46, 55)	NR	Moderate
Nedocromil sodium vs. Sodium cromoglycate	N=7 (97 vs. 97) 0.9 (-2.7, 4.5)	N=6 (78 vs. 78) 1.12 (0.89, 1.40)	NR	≤10% fall FEV_1 N=6 (78 vs. 78) 1.0 (0.7, 1.4)	Moderate
MCS vs. Anticholinergics	N=8 (183 vs. 175) 6.7 (3.3, 10.0)	N=5 (56 vs. 48) 1.35 (1.00, 1.83)	11.2 (2.4, 20.0)	≤15% fall FEV_1 N=8 (177 vs. 169) 1.3 (1.1, 1.6)	Moderate
SABA vs. MCS	N=12 (271 vs. 272) 6.8 (4.5, 9.2)	N=6 (77 vs. 77) 1.4 (1.1, 1.7)	22.7 (11.9, 33.4)	≤15% fall FEV_1 N=9 (225 vs. 226) 1.4 (1.2, 1.8)	Moderate
SABA + MCS vs. SABA	N=5 (40 vs. 40) 1.3 (-6.3, 8.9)	N=3 (37 vs. 37) 0.9 (0.7, 1.1)	10.3 (-27.0, 6.5)	≤15% fall FEV_1 N=4 (44 vs. 44) 0.9 (0.5, 1.4)	Moderate
LABA vs. Placebo	N=4 (55 vs. 55) 25.1 (18.0, 32.3)	NR	86%	NR	Moderate
Anticholinergics (Ipratropium bromide) vs. placebo	N=11 (142 vs. 142) 9.8 (5.0, 19.5)	N=6 % achieved=60 (48, 72)	NR	≤10% fall FEV_1 N=7 (74 vs. 74) 4.5 (1.2, 10.9)	Moderate
Interval warmup vs. no warmup	N=4 (56 vs. 56) 10.6 (6.5, 14.7)	NR	NR	≤15% fall FEV_1 N=1 1/12 (8.3%)	Low
Continuous low intensity warmup vs. no warmup	N=3 (37 vs. 37) 12.6 (-1.5, 26.7)	NR	NR	≤15% fall FEV_1 N=1 6/12 (50%)	Low
Continuous high intensity warmup vs. no warmup	N=2 (13 vs. 13) 9.8 (-6.4, 26.0)	NR	NR	NR	Low

BUD = budesonide; BV =Betamethasone valerate; FEV1 = forced expiratory flow in 1 second; FP=fluticasone ICS = Inhaled corticosteroid; LTRA = leukotriene receptor antagonist; MCS = mast cell stabilizers; MD = mean difference; NR = not reported; PEF = peak expiratory flow; RR = risk ratio; SABA = short-acting beta-agonist; SSi = sample size intervention; SSc = sample size comparison

*a positive MD indicates intervention is better; † RR>1 indicates intervention is better.

Pharmacologic Interventions

Bronchodilating Agents

SABA/LABA. Beta$_2$-receptors on the airway smooth muscle are responsible for bronchodilation; beta$_2$-agonist agents attach to these receptors and are effective bronchodilators. SABA agents have been the mainstay of EIB/EIA prevention and treatment for many years. With the development and availability of LABA agents, more research has been applied to their effectiveness in EIB/EIA.

Although the evaluation of SABA or LABA versus placebo for prophylactic EIB/EIA use was not the focus of this review, results were available in some comparisons on which to base a reasonable conclusion. In the mast cell stabilizer (MCS) review[78] SABA agents were approximately 7.0 percent more effective than MCS. Using data from the SABA groups in the 12 studies in the comparison with MCS,[78] SABA reduced the maximum percent fall in FEV_1 to an average of 4.3 percent (SD±14.1; range 1.0 to 15.5) whereas as the MCS groups averaged a maximum percent fall in FEV_1 of 11.0 percent (SD±17.7; range 4.2 to 27.2).[78] The day 1 data for the four LABA groups in the tachyphylaxis review showed that LABA reduced the fall in FEV_1 to an average of 3.7 percent (SD±8.7). This indicates that LABA is also an effective agent for attenuating the bronchoconstriction that is characteristic of EIB/EIA (Figure 28).

While SABA and LABA treatments are effective, caution is advised. The data from this review support that a degree of tachyphylaxis is associated with the regular use of both beta-agonist agents. The pooled results from four LABA trials demonstrated the maximum percent fall in FEV_1 following an ECT after 4 weeks of regular LABA use was of a greater magnitude in the LABA arm than the placebo arm. Similar results were shown in the two studies that investigated SABA after only 1 week of regular use. While the results were statistically significant, there was no discussion on whether this was clinically significant or important to the participants. These data do not imply that SABA or LABA agents lose their effectiveness altogether following regular use; however, the magnitude of their effectiveness is reduced. There are no data on whether the tolerance to these agents continues to increase as duration of regular use increases to several months.

Short-acting anticholinergic (SAAC) agents. Anticholinergic agents are used in respiratory conditions to decrease mucus production and as weak bronchodilators. The original SAAC agent used in asthma was atropine; however, ipratropium bromide (IB; Atrovent™) and oxitropium bromide (OB; Oxivent™) are more commonly used. Long-acting anticholinergics such as tiotropium (Spiriva®) are available; however, they are more commonly used in the management of chronic obstructive pulmonary disease. SAAC agents are an intuitive addition to the treatment regimen given the concerns regarding the potential for tachyphylaxis with regular use of SABA and LABA agents.

We identified 18 trials (211 patients enrolled) that compared SAAC agents with placebo in single-dose prophylactic treatment of EIB/EIA. Twelve of the 18 researched IB and, given the worldwide availability and use of this drug, the discussion focuses on this agent.

The pooled results demonstrated a consistent benefit attributable to IB (Table 42 and Figure 28). The maximum percent fall in FEV_1 at an ECT less than 2 hours following treatment was reduced by approximately 12 percent (17 percent in PEF) compared with placebo. These clinically relevant results, however, are tempered by the presence of moderate heterogeneity.

Complete protection was achieved 4.5 times more often with IB than placebo. This conclusion is strengthened by the negligible heterogeneity (I^2=0 percent). Only four of 18 studies reported side effects; there were no differences identified between IB and placebo. Despite the theoretical autonomic nervous system risks associated with use of SAAC agents (e.g., dry mouth, glaucoma, confusion), there is sufficient evidence from the acute respiratory literature to suggest that a single dose of IB is safe in patients with EIA.[168,169]

From the available evidence, it appears that when used as a pre-exercise treatment IB can be effective and safe for patients with EIB/EIA. The strength of the body of evidence is moderate.

Anti-inflammatory Agents

Mast cell stabilizers (MCS). Mast cells are important cellular contributors to the inflammatory cascade seen in asthma. MCS are asthma agents that stabilize the mast cell and prevent the release of inflammatory mediators. They are used as weak anti-inflammatory agents in mild to moderate chronic asthma. We identified three existing Cochrane reviews that addressed MCS as prophylactic treatment for EIA (Table 42 and Figure 28). The first review[76] included 21 trials that studied a single prophylactic dose of nedocromil sodium (NCS) in doses ranging from 1 mg to 8 mg, compared with a placebo. The second review[77] (9 trials) compared the effects of a single prophylactic dose of NCS, in doses ranging from 2 mg to 8 mg, to one of sodium cromoglycate (SCG), in doses ranging from 10 mg to 20 mg. The summary data from this review failed to identify differences with respect to the maximum percent decrease in FEV_1, complete protection, or the degree of clinical protection between the two drugs. Given this result, the third review[78] included trials that compared either NCS or SCG (collectively called MCS) to an anticholinergic agent (n=11), a SABA alone (n=20), or a combination of a SABA and MCS (n=10).

All studies in these three reviews included RCTs conducted on children (6 to 17 years) and adults (18 years and older) with stable asthma who experienced EIA. The majority of studies employed a crossover design with adequate time between ECTs to eliminate carryover effects but avoid period effects.

In people with stable asthma that experience EIA, NCS taken 15 to 60 minutes prior to exercise significantly reduced the severity of EIA in both children and adults. Regardless of dose, timing, delivery method, or age, NCS provided a clinically significant benefit that was 51 percent greater than placebo. The average post-exercise percent fall in FEV_1 across the 16 studies after NCS was 15.6 percent (range 10 to 29.8) compared with a fall of 30.2 (range 20.8 to 48.1) on placebo (MD=15.6 percent; 95 percent CI: 13.2, 18.1). There was substantial heterogeneity in this result that was eliminated when subgroups based on severity of EIA were compared. The benefit from NCS was more pronounced in those with severe EIA (fall in FEV_1 of 30 percent or greater).

When either NCS or SCG was compared to anticholinergics the data indicated MCS agents were somewhat more effective than anticholinergics but not as effective as SABA agents. The combination of SABA and MCS agents did not provide significant advantages over a SABA alone. Data on the safety of these agents were not routinely reported, but when it was, no serious side effects were observed. The strength of the body of evidence is moderate.

Inhaled corticosteroids (ICS). The main anti-inflammatory agents used for chronic and acute asthma management are ICS, either alone or in combination with LABA agents. ICS agents are used in respiratory conditions to decrease inflammation and reduce mucus production;

they have no direct bronchodilating effects. Contrary to systemic corticosteroids, ICS are inhaled and exert their effects locally; little of the available drug is absorbed into the systemic circulation. There are a large number of ICS agents available on the North American market (in alphabetical order): beclomethasone (QVAR™), budesonide (Pulmicort™), flunisolide (Aerobid™), fluticasone (Flovent™), and triamcinolone (Azmacort™). Agents also exist that combine ICS with LABA in one inhaler (in alphabetical order): budesonide and formoterol (Symbicort™) and fluticasone and salmeterol (Advair™). Koh et al.[107] published a systematic review involving six studies comparing 4 to 12 weeks of daily ICS use with placebo for prevention of EIB/EIA. The reviewers concluded that 4 or more weeks of daily ICS use attenuated the fall in FEV_1 in ranges of 7 to 14 percent over placebo. There was not enough data at that time to assess ICS used as a single-dose prophylactic for EIB/EIA. We identified four trials involving 50 children and adults that did so. Though the methodological quality of the studies was moderately good, questions remain on how adequately they were randomized and double blinded.

Although the pooled results presented here favor ICS, they failed to demonstrate a statistically or clinically beneficial reduction in the maximum percent fall in FEV_1 or PEF compared with placebo (Table 42 and Figure 28). No sound conclusions could be drawn on the complete or clinical protection provided by ICS either. None of the studies reported adverse effects. Despite the theoretical risks associated with ICS use, there is sufficient evidence from the acute respiratory literature to suggest that a single dose of ICS is safe in patients with EIB/EIA. Adverse effects such as cataracts,[170] adrenal suppression, osteoporosis and fractures,[171] occur with long-term use; they are not likely an issue of concern with episodic use.

From the available evidence we cannot conclude that pre-treatment with ICS agents is an effective and safe strategy for patients with EIB/EIA. The strength of the body of evidence is moderate.

Leukotriene receptor antagonists (LTRA). Leukotrienes are produced by the cysteinyl leukotriene pathway and are implicated in both bronchoconstriction and in the inflammatory cascade leading to worsening asthma. LTRAs, which block this pathway, are available for the management of chronic and acute asthma.

We identified nine trials involving 535 patients and 10 comparisons of prophylactic treatment of EIA with LTRA compared with placebo. The methodological quality of the studies was reasonably strong. The pooled results demonstrated a consistent though modest benefit in favor of LTRAs. LTRAs were superior to placebo and reduced (i.e., improved) the percent fall in FEV_1 at the earliest measurement (usually less than 2 hours) by approximately 9 percent compared with placebo (Table 42 and Figure 28). The protective effect of this pre-treatment extended up to the 8 and 24 hour measurements of FEV_1 when there was a 7 and 5 percent improvement over placebo, respectively. It is likely that the weak anti-inflammatory effect of LTRAs is responsible for this extended action. These results are tempered by the presence of moderate heterogeneity (50 to 70 percent) in all meta-analyses. Few studies reported side effects and the data that were reported identified no differences between LTRAs and placebo; however, there is sufficient evidence from the chronic asthma literature to suggest that LTRAs are safe.[172]

From the available evidence, it appears that LTRAs can be somewhat useful and safe as pre-exercise treatment for patients with EIB/EIA. The strength of the body of evidence is moderate.

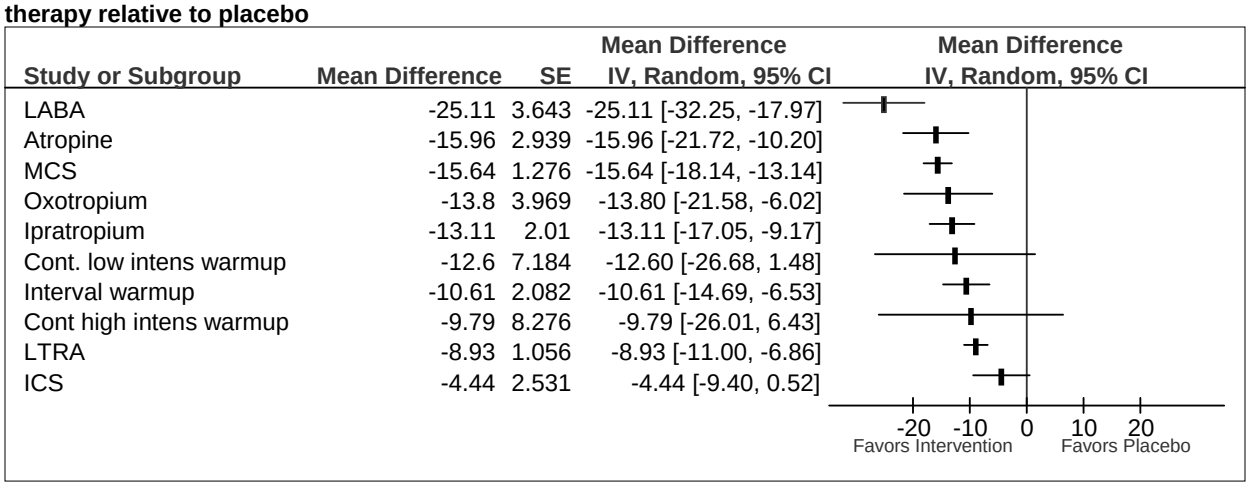
Nonpharmacologic Interventions

As an alternative to drug interventions to attenuate and/or prevent EIB/EIA, many athletes, trainers and researchers advocate specific warmup exercises as a method to achieve similar results. We identified seven trials involving 128 patients that compared various forms of warmup activities to no warmup in the pre-exercise treatment of EIB/EIA. Convincing conclusions cannot be made regarding warmups because results are tempered by the methodologically poor quality of the studies and the variability in the warmup protocols studied.

Three general approaches were examined: interval, continuous high intensity (two standardized exercise challenges 45 minutes apart), and continuous low intensity (treadmill runs at work rates of 60 percent). The pooled results varied (Table 42 and Figure 28). Compared with no warmup, interval warmups attenuated the fall in FEV_1 following a subsequent ECT by a statistically significant 11 percent. For both high and low intensity continuous warmups, there was a 10 to 12 percent improvement in FEV_1 but it was not statistically significant and it was associated with substantial heterogeneity. Combinations of various warmup protocols within studies also demonstrated protection against EIB/EIA with an attenuating factor between 10 and 11 percent. Eck et al.[98] reported that 79 percent of participants achieved protection (but did not designate a cutpoint for this) when a combination of warmup activities was used as a pre-treatment for EIB/EIA. Pooling the study data was not possible due to the heterogeneity of the warmup protocols.

From this evidence, it appears that certain warmup protocols are effective at reducing the degree of airway obstruction associated with EIB/EIA. Combination warmups show promise; however, it is unclear whether continuous warmups are effective in this condition. The strength of the body of evidence is low.

Figure 28. Mean difference in the maximum percent decrease in FEV_1 following ECT with prophylactic therapy relative to placebo



NOTE: The reduction in FEV_1 post-exercise challenge with prophylactic therapy was compared with FEV_1 post-exercise challenge with placebo (i.e. placebo response - prophylactic response), and therefore negative values favor the prophylactic pre-treatment.

Limitations

In addition to the methodological issues identified previously regarding trial designs in EIB/EIA, there are several limitations that need to be discussed regarding systematic reviews. First, there is a possibility of publication bias in this systematic review. By missing unpublished and/or negative therapy studies, we may be overestimating the therapeutic benefits of certain interventions. A comprehensive and systematic search of the published literature for potentially relevant studies was conducted to avoid publication bias. This was supplemented by searching for gray literature (i.e., unpublished or difficult to find studies. Despite these efforts, we recognize that we may have missed some of these types of studies.

There is also a possibility of study selection bias. However, we employed at least two independent reviewers and feel confident that the studies that were excluded from this report were done so for consistent and appropriate reasons. Our search was comprehensive, so it is unlikely that there are many studies in press or publication that were missed.

There are several other issues with respect to populations, interventions, outcome assessments, and controls that require discussion.

Population. In general the populations involved in the therapy trials were volunteer recruits from hospital and outpatient clinics or schools for asthmatic children. All had confirmed asthma and documented EIA. The lack of reporting certain baseline data precluded more detailed subgroup analysis that would be of interest to the medical community. Larger sample sizes would help to provide more conclusive results. Overall, we do not believe these limitations invalidate the results presented in the therapy review as the reviewers analyzed the data as vigorously as was possible.

Intervention. Despite the variation in dose, delivery method, and timing of prophylactic drug treatment, these studies employed RCT methodology and standardized the drug interventions that were investigated. The major limitations are the small sample sizes and small number of trials that investigated each drug category. The interventions investigating warmup protocols were not standardized across trials. While we divided the warmup interventions into three groups based on the level of intensity required, each warmup approach varied considerably from study to study. Overall, we do not believe these limitations invalidate the results presented in the review; however, they do limit robust interpretation, drawing firm conclusions, and generalization of results.

Control. Many of the patients in the pharmacologic studies were administered placebo agents as the control treatment. These agents were often similar in appearance or delivery; however, it may have been possible for patients to detect differences among treatments, especially the bronchodilators such as SABA, LABA and SAAC agents. Also, the studies used a range of placebo devices and propellants, some of which provided significant protection to a large proportion of participants in the study. It was not possible to blind the participants to the warmup protocols in the refractory studies and it was not reported if the purpose of the intervention was known to them. Furthermore, blinding of the person conducting and assessing spirometry following the intervention and the ECT was rarely reported. It is impossible to determine how this might have affected the results. None of the included studies reported the patient's perception of treatment received. Overall, we do not believe these limitations invalidate the results presented in the review; however, they do raise questions surrounding the lack of blinding and how that may affect estimates of the overall treatment effect.[13]

Outcome. The pulmonary function outcomes reported were not standardized and comprised various forms of FEV_1 and PEF measures. Some could not be transformed or calculated from individual patient data and therefore were not included in a pooled analyses. Also, the maximum percent fall in FEV_1 cutpoints to confirm EIB/EIA ranged from a fall of 10 to 20 percent. The ATS convention is to accept a 10 percent fall in FEV_1, and that was what was employed in the majority of studies.

Outcome reporting always included a pulmonary function measure following the intervention and ECT. However, reporting other useful outcomes such as clinical and complete protection data was not consistent (Table 42). Wherever possible, we calculated these results from IPD. Few secondary outcomes were reported. For example, patient preference for the intervention, effect on performance, effect on signs and symptoms were absent. Side effect profiles were also poorly reported; however, sufficient evidence exists for the safety of many of these agents from the chronic asthma literature. Overall, we do not believe these limitations invalidate the results of the therapy review.

Finally, the comparative effectiveness of these treatments is difficult to determine. There are few direct comparisons among specific interventions for EIB/EIA treatments and this makes decisionmaking for patients and clinicians problematic. The indirect comparisons provided in Figure 28 are to be used with caution.

Conclusions

Despite exhaustive efforts to identify evidence regarding therapeutic effectiveness of various interventions used to treat people with EIB/EIA, only a small number of studies met the inclusion criteria for each key question. All of the studies recruited people with asthma and reproducible EIA. Evaluation of therapeutic effect on EIB was not possible. Many of the studies suffered from potential biases. Nonetheless, this summary represents the most comprehensive review of therapies for EIA published to date.

On the basis of this review, we can conclude that all bronchodilators that were examined are effective at attenuating and even preventing the FEV_1 drop associated with EIA (Figure 28). There is emerging evidence of the development of tachyphylaxis associated with daily use of SABA and LABA agents. This suggests that SABA and LABA agents should be used only "as required," rather than regularly, in order to preserve their use as prophylactic agents for EIA. SAAC agents were found to be effective pre-EIA bronchodilator agents.

We can conclude that the anti-inflammatory agents examined provide mixed results. For example, MCS agents are very effective in attenuating or eliminating the FEV_1 drop associated with EIA. There is some role for LTRA in the treatment of EIA; however, the attenuation of EIA appears less than with other anti-inflammatory agents. There is limited evidence of a benefit associated with pre-treatment with ICS compounds. The long-term benefit of ICS agents in asthma is no longer questioned,[107] and it is possible that better control of chronic airway inflammation may benefit patients with EIA specifically.

Finally, pre-exercise interval warmup appears to be useful in significantly attenuating or eliminating the FEV_1 falls associated with EIA. This set of interventions requires further research on the relative effectiveness of various types of warmup.

Recommendations for Future Research

Efforts are needed to improve the overall quality of reporting of primary studies of diagnostic test accuracy. The STARD checklist[105] details 25 items that address the level of detail that should be specified within such studies including descriptions of participants, tests methods, statistical methods, and results. This could be considered as a guide for authors reporting studies that evaluate diagnostic tests and for journals that publish EIB/EIA-related research.

Studies designed to more carefully examine the methodology of the standard ATS ECT test are needed. Specifically, guidelines state that the inspired air temperature must be less than 25^{o}C, and less than 50 percent relative humidity. Studies have used inspired air as cold as -18^{o}C and many have used medical compressed air, which has a relative humidity of 0 percent as the air leaves the tank. Colder, drier air would result in the greatest increase in osmolarity of the airway surface and thus most likely cause EIB/EIA. Additional studies are needed to more thoroughly examine how inspired air affects EIB/EIA so that a more standardized ECT guideline can be developed.

Future purposely designed studies to compare the diagnostic characteristics of different diagnostic methods are needed. New tests such as mannitol are encouraging; however, currently there are insufficient data to allow for a strong recommendation of this test. Particular attention in future studies must be given to including a representative sample of participants with suspected EIB/EIA. Studies that prospectively recruit participants and blind the reference standard results to those who interpret the index test results are needed.

To determine if the response to diagnostic tests differs in those with EIB versus EIA, those with atopy or no atopy, or other potentially defining characteristics, appropriate populations need to be included, adequate baseline data reported, and comparative analyses by the characteristics of interest performed and reported.

With regard to the systematic review of therapy for EIA, there are several issues with respect to methodological quality, populations, interventions, outcome assessments, and controls that require discussion.

Efforts are needed to improve the quality of reporting primary studies (i.e., randomized controlled trials). The CONSORT Statement[106] could be considered as a guide for authors reporting trials and journals that publish EIB/EIA-related research. Most trials in this review used a crossover design. Concerns regarding crossover trials center on three factors: drug carryover effects, period effects, and statistical issues. Data should be reported in a manner that allows analyses to confirm the presence or absence of a carryover effect. Future studies should focus on complete reporting of results by period and sequence to assure readers that these concerns have been accounted for.

Population: The populations involved in the therapy trials all had stable asthma and confirmed EIA. Athletic status was not reported. This finding, coupled with the small number of studies investigating some interventions, precluded more detailed subgroup analysis of the issue of EIB/EIA in elite athletes. Additional investigations of treatment effects in patient subgroups defined by asthma severity, age, and activity level are clearly indicated.

More trials in clinically homogenous groups of patients with EIB and patients with EIA are needed to better explore and characterize differences in the efficacy of interventions between these two conditions.

Intervention: The nonpharmacologic interventions were not standardized. Although the warmup interventions were divided into similar groups, each warmup approach varied from the others. Future research exploring different standardized warmup approaches is clearly indicated.

Control: Many of the patients in the pharmacological studies were administered placebo agents as the control treatment. These agents were often similar in appearance or delivered in similar appearing devices (inhaler agents) to the active treatment; however, it may have been possible for patients to detect differences among treatments, especially the bronchodilators such as SABA, LABA and SAAC agents. It is impossible to determine how frequently this occurred since most studies did not report the patient's perception of treatment received. In addition, it was not possible to blind the participants to the warmup programs in the refractory studies. When the participant cannot be blinded, it is particularly important that the outcome assessor be blinded to all information that could bias the outcome measure or assessment (e.g., other test results, intervention given, challenge performed).

Outcome: The pulmonary function outcomes reported varied and studies used different diagnostic cutpoints ranging from a fall index of 10 to 20 percent. The ATS convention is to accept a 10 percent maximum fall in $FEV_{1.}$ While outcome reporting included detailed pulmonary function measures, the format was not standardized. Data on the proportion obtaining clinical and complete protection were often missing (Table 2).

Side effect profiles were also poorly reported. While there is evidence for the safety of many of these agents from the chronic asthma literature, it would be prudent for future research to capture adverse effects in the EIB/EIA population. Future trials of interventions to prevent or attenuate EIB/EIA should include clinically relevant secondary outcomes such as patient preferences, symptom scores, and sport performance effects (e.g., changes in athletic performance or endurance). More robust outcome reporting would further inform decision-making by athletes, physicians, and sporting bodies.

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Abbreviations

95% CI	95 percent confidence interval
ATS	American Thoracic Society
AUC	Area under the curve
BI	Bronchoprotection index
C	Centigrade
CCT	Clinical controlled trial
CO_2	Carbon dioxide
ECT	Exercise challenge test
EIA	Exercise induced asthma
EIB	Exercise induced bronchoconstriction
EVH	Eucapnic voluntary hyperpnea
FEV_1	Forced expiratory volume in 1 second
FRAST	Free running asthma screening test
GRADE	Grading of Recommendation, Assessment, Development, and Evaluation
IB	Ipratropium bromide
ICS	Inhaled corticosteroid
IPD	Individual patient data
IQR	Inter-quartile range
LABA	Long-acting beta-agonist
LTRA	Leukotriene receptor antagonist
MCH	Methacholine challenge
MCS	Mast cell stabilizer
MD	Mean difference
MDI	Metered-dose inhaler
Mg/ml	Milligrams per millilitre
mg	Milligram
MVV	Maximum voluntary ventilation
NCS	Nedocromil sodium
NSAIDS	Nonsteroidal anti-inflammatory drugs
O_2	Oxygen
OB	Oxitropium bromide
PC_{20}	Provocative concentration causing a 20 percent fall in FEV_1
PEF	Peak expiratory flow
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy
RCT	Randomized controlled trial
RH	Relative humidity
ROC	Receiver operating characteristic
RR	Risk ratio
SAAC	Short-acting anticholinergic
SABA	Short-acting beta-agonist
SCG	Sodium cromoglycate
SD	Standard deviation
SE	Standard error
STARD	Standard of Reporting of Diagnostic Accuracy

TEP	Technical expert panel
VATAP	Veterans Affairs Technology Assessment Program
VO_{2max}	Maximum oxygen consumption

Appendix A. Technical Expert Panel and Peer Reviewers

Technical Expert Panel

In designing the study questions and methodology, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Due to these differences in opinion, the study questions, design, and/or methodologic approaches do not necessarily represent the views of individual technical and content experts.

Technical Expert	Affiliations/Location
Louis-Philippe Boulet, M.D., F.R.C.P.C.	Université Laval and Hôpital Laval Sainte-Foy, QC
Robert Cowie, M.D., F.C.P.(S.A.), M.Sc.	University of Calgary Calgary, AB
Andrew Gregory, M.D., F.A.A.P., F.A.C.S.M.	Vanderbilt University Medical Center Nashville, TN
Cynthia LaBella, M.D.	Children's Memorial Hospital Chicago, IL
Darcy Marciniuk, M.D., F.R.C.P.C.	University of Saskatchewan Saskatoon, SK
Kenneth Rundell, Ph.D.	Marywood University Scranton, PA

Peer Reviewers

Peer reviewer comments on a preliminary draft of this report were considered by the EPC in preparation of the final report. The synthesis presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewer	Affiliations/Location
Louis-Philippe Boulet, M.D., F.R.C.P.(C.)	Université Laval and Hôpital Laval Sainte-Foy, QC
Robert Cowie, M.D., F.C.P.(S.A.), M.Sc.	University of Calgary Calgary, AB
Andrew Gregory, M.D., F.A.A.P., F.A.C.S.M.	Vanderbilt University Medical Center Nashville, TN
Kenneth Rundell, Ph.D.	Marywood University Scranton, PA
Jeannette May	Representative, Disease Management Association of America Washington, DC
H. William Kelly, Pharm.D.	University of New Mexico Albuquerque, NM
Sheldon Spector, M.D. & Ricardo Tan, M.D.	California Allergy & Asthma Medical Group Los Angeles, CA
John Weiler, M.D.	American Academy of Asthma Allergy and Immunology Iowa City, IA

Appendix B. Literature Search Strings

Table B1. Diagnosis of EIB/EIA review – OVID Databases

Search Date: November 20, 2008
Number of Results: 3640

Database	Years Searched	Number of Results
AMED (Allied and Complementary Medicine)	1985 to November 2008	21
PsycINFO	1806 to November Week 3 2008	14
MEDLINE®	1950 to November Week 2 2008	2321
EMBASE	1988 to 2008 Week 46)	1006
PASCAL	1987 to October 2008	179
EBM Reviews - Cochrane Central Register of Controlled Trials	4th Quarter 2008	99

MULTIFILE STRATEGY

1. exp "Exercise Induced Asthma"/ or exp Asthma, Exercise-Induced/
2. ("induced bronchoconstriction" or "induced asthma" or "induced bronchospasm").kw,ie,id,sh. and (exercise* or (train* and (military or army)) or fitness or "physical activity" or exertion or athlet* or sport*).mp.
3. (bronchoconstrict* or asthma* or antiasthma* or wheez* or (respiratory adj sound?) or (bronchial adj5 (spasm* or constrict*)) or bronchospas* or "bronchial hyperreactivity" or "respiratory hypersensitivity").mp.
4. ((bronchial* or respiratory or airway* or lung*) adj5 (hypersensitiv* or hyperreactiv* or allerg* or insufficiency)).mp.
5. or/3-4
6. (EIB or EIA).ti,ab.
7. ((exercise adj5 induced) or "exercised-induced" or (exercise adj5 challenge) or "exercise tolerance" or "physical exercise" or (train* and (military or army)) or fitness or "physical activity" or exertion or athlet* or sport*).mp,jn. or exp Sports/ or Exercise/
8. or/6-7
9. and/5,8
10. or/1-2,9
11. (sensitiv* or diagnos* or predictive value* or probability).mp.
12. (accurac* or specificity).tw.
13. ((pre-test or post-test) adj probability).mp.
14. likelihood ratio*.mp.
15. di.fs.
16. *Diagnostic Accuracy/
17. (mannitol or methacholine or MCT or EVH or eucapnic or hyperpnea* or FRAST or provocation or marker* or screen* or test*).mp.
18. or/11-17
19. 18 and 10
20. limit 19 to english language
21. limit 20 to human
22. remove duplicates from 21

Table B2. Diagnosis of EIB/EIA review – EBSCO Databases

Search Date: November 17, 2008
Number of Results: 905

Database	Years Searched	Number of Results
CINAHL® (Cumulative Index to Nursing & Allied Health Literature)	1937 to 2008	280
SPORTDiscus with Full Text	1800 to 2008	246
Academic Search Elite	1985 to 2008	379

MULTIFILE STRATEGY

S1 (DE "EXERCISE" OR DE "ABDOMINAL exercises" OR DE "AEROBIC exercises" OR DE "AQUATIC exercises" OR DE "ARM exercises" OR DE "BACK exercises" OR DE "BREATHING exercises" OR DE "BREEMA" OR DE "BUTTOCKS exercises" OR DE "CALLISTHENICS" OR DE "CHAIR exercises" OR DE "CIRCUIT training" OR DE "EXERCISE therapy" OR DE "FACIAL exercises" OR DE "FALUN gong exercises" OR DE "GYMNASTICS" OR DE "HAND exercises" OR DE "HATHA yoga" OR DE "ISOKINETIC exercise" OR DE "ISOMETRIC exercise" OR DE "LEG exercises" OR DE "LIANGONG" OR DE "METABOLIC equivalent" OR DE "MU-lan chuan" OR DE "MUSCLE strength" OR DE "PHYSICAL fitness" OR DE "PHYSICAL fitness for men" OR DE "PILATES method" OR DE "PLYOMETRICS" OR DE "QI gong" OR DE "REDUCING exercises" OR DE "RUNNING" OR DE "SCHOOLS -- Exercises & recreations" OR DE "SEXUAL exercises" OR DE "SHOULDER exercises" OR DE "STRETCHING exercises" OR DE "TAI chi chuan" OR DE "TREADMILL exercise") or (DE "SPORTS" OR DE "AERONAUTICAL sports" OR DE "AGE & sports" OR DE "AQUATIC sports" OR DE "BALL games" OR DE "BASEBALL" OR DE "BASKETBALL" OR DE "CHARITY sports events" OR DE "COLLEGE sports" OR DE "DISCRIMINATION in sports" OR DE "DOPING in sports" OR DE "ENDURANCE sports" OR DE "EXTREME sports" OR DE "FASCISM & sports" OR DE "FEMINISM & sports" OR DE "FOOTBALL" OR DE "GAELIC games" OR DE "GAY Games" OR DE "GAYS & sports" OR DE "GLBT people & sports" OR DE "GLBT rodeos" OR DE "GOLF" OR DE "GOODWILL Games" OR DE "GROUP games" OR DE "GYMNASTICS" OR DE "HOCKEY" OR DE "HOMOPHOBIA in sports" OR DE "INDIVIDUAL sports" OR DE "KNIFE throwing" OR DE "LESBIANS & sports" OR DE "LOG-chopping (Sports)" OR DE "MASCULINITY in sports" OR DE "MASS media & sports" OR DE "MILITARY sports" OR DE "MINORITIES in sports" OR DE "MOTION pictures in sports" OR DE "MOTORSPORTS" OR DE "NATIONAL socialism & sports" OR DE "NATIONALISM & sports" OR DE "OLYMPICS" OR DE "PARKOUR" OR DE "PRESIDENTS -- Sports" OR DE "PRESIDENTS -- United States -- Sports" OR DE "PROFESSIONAL sports" OR DE "PROFESSIONALISM in sports" OR DE "RACING" OR DE "RACISM in sports" OR DE "RACKET games" OR DE "ROBOTICS in sports" OR DE "RODEOS" OR DE "ROLLER skating" OR DE "SCHOOL sports" OR DE "SENIOR Olympics" OR DE "SEX discrimination in sports" OR DE "SEXUAL harassment in sports" OR DE "SHOOTING" OR DE "SHUTOUTS (Sports)" OR DE "SOCCER" OR DE "SOCIALISM & sports" OR DE "SPORT for All" OR DE "SPORTS & tourism" OR DE "SPORTS -- Collectibles" OR DE "SPORTS -- Corrupt practices" OR DE "SPORTS -- Economic aspects" OR DE "SPORTS -- Finance" OR DE "SPORTS -- Songs & music" OR DE "SPORTS for children" OR DE "SPORTS for people with disabilities" OR DE "SPORTS for women" OR DE "SPORTS forecasting" OR DE "SPORTS rivalries" OR DE "SPORTS teams" OR DE "STEREOTYPES (Social psychology) in sports" OR DE "TARGETS (Sports)" OR DE "TEAMWORK (Sports)" OR DE "TELEVISION & sports" OR DE "TOMAHAWK throwing" OR DE "TRACEURS" OR DE "VIDEO tapes in sports" OR DE "VIOLENCE in sports" OR DE "WINTER sports")

S2 (MH "Sports+") or (MH "Physical Fitness") or (MH "Exercise+")

S3 exerc* OR train* OR fitness OR physical OR athlet* OR sport*

S4 S3 or S2 or S1

S5 (bronchial* OR respiratory OR airway* OR lung*) and (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficiency)

S6 bronchoconstrict* OR asthma* OR antiasthma* OR wheez* OR "Respiratory Sounds" OR "Bronchial Spasm" OR bronchospas* OR "Bronchial Hyperactivity" OR "Respiratory

	Hypersensitivity"
S7	DE "BRONCHIAL spasm"
S8	(MH "Bronchoconstriction")
S9	(MH "Asthma")
S10	(bronch* AND spasm*) or (bronch* AND constrict*)
S11	S10 or S9 or S8 or S7 or S6 or S5
S12	S11 and S4
S13	DE "EXERCISE-induced asthma"
S14	(MH "Asthma, Exercise-Induced")
S15	S14 or S13 or S12
S16	diagnos* OR specificity OR accurac* OR predictive OR sensitiv* OR probability OR likelihood
S17	S16 and S15
S18	S16 and S15 *Limiters - Exclude MEDLINE records; Language: English*

Table B3. Diagnosis of EIB/EIA review – Web of Science® - Institute for Scientific Information – Thomson Reuters

Years/issue searched: 1900 to 2008 **Search date**: November 17, 2008 **Number of Results**: 984
TS=((exerc* OR train* OR fitness OR "physical activity" OR athlet* OR sport*) AND (bronchoconstrict* OR asthma* OR antiasthma* OR wheez* OR "Respiratory Sounds" OR "Bronchial Spasm" OR bronchospas* OR "Bronchial Hyperreactivity" OR "Respiratory Hypersensitivity" OR (bronch* AND spasm*) OR (bronch* AND constrict*) OR (bronchial* OR respiratory OR airway* OR lung*) AND (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficiency))) AND TS=(diagnos* OR sensitiv* or predictive OR accurac* OR specificity OR probability OR likelihood) AND Language=(English) AND Document Type=(Article OR Meeting Abstract OR Meeting-Abstract OR Proceedings Paper)

Table B4. Diagnosis of EIB/EIA review – BIOSIS PREVIEWS® - Institute for Scientific Information – Thomson Reuters

Years/issue searched: 1926 to 2008 **Search date**: November 17, 2008 **Number of Results**: 1317
#1 Topic=(diagnos* OR sensitiv* or predictive OR accurac* OR specificity OR likelihood OR probability) #2 Topic=(exerc* OR train* OR fitness OR "physical activity" OR athlet* OR sport*) #3 TS=(bronchial* OR respiratory OR airway* OR lung*) SAME TS=(hypersensitiv* OR hyperreactiv* OR allerg* OR insufficiency) #4 TS=(bronchoconstrict* OR asthma* OR antiasthma* OR wheez* OR "Respiratory Sounds" OR "Bronchial Spasm" OR bronchospas* OR "Bronchial Hyperreactivity" OR "Respiratory Hypersensitivity" OR (bronch* SAME spasm*) OR (bronch* SAME constrict*)) #5 #3 OR #4 #6 #1 AND #2 AND #5 AND Language=(English) AND Document Type=(Article OR Book Chapter OR Meeting OR Meeting Paper OR Technical Report OR Thesis Dissertation) AND Taxa Notes=(Humans) #7 TI=COPD NOT TI=asthma* #8 #6 NOT #7

Table B5. Diagnosis of EIB/EIA review – PubMed: National Library of Medicine

Years/issue searched: 1950 to 2008 **Search date**: November 25, 2008 **Number of Results**: 138
("diagnosis"[MeSH Subheading] OR diagnos* OR sensitiv* OR predictive OR accurac* OR specificity OR probability OR likelihood OR mannitol OR methacholine) AND ((((bronchoconstrict* OR asthma* OR antiasthma* OR wheez* OR "Respiratory Sounds" OR "Bronchial Spasm" OR bronchospas* OR "Bronchial Hyperreactivity" OR "Respiratory Hypersensitivity") OR (bronch* AND (spasm* OR constrict*)) OR ((bronchial* OR respiratory OR airway* OR lung*) AND (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficiency))) AND (exerc* OR train* OR fitness OR "physical activity" OR athlet* OR sport*)) OR ((EIB OR EIA) AND (asthma* OR bronch*))) Limits: *added to PubMed in the last 1 year, English*

Table B6. Diagnosis of EIB/EIA review – Scopus®: Elsevier

Years/issue searched: 1823 to 2008 **Search date**: November 14, 2008 **Number of Results**: 1466
TITLE-ABS-KEY(diagnos* OR sensitiv* OR predictive OR accurac* OR specificity OR probability OR likelihood OR methacholine OR mannitol OR screen* OR test*) AND TITLE-ABS-KEY-AUTH(exercise induced asthma) AND (LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip"))

Table B7. Diagnosis of EIB/EIA review – Medion database of diagnostic reviews - University of Maastricht

Years/issue searched: 1967 to 2008 **Search date**: November 28, 2008 **Number of Results**: 0
Asthma , eia, eib, exercise

Table B8. Diagnosis of EIB/EIA review – Proquest Dissertations and Theses

Years/issue searched: 1861 to 2008 **Search date**: November 13, 2008 **Number of Results**: 25
(bronchoconstrict* OR asthma* OR antiasthma* OR wheez* OR "Respiratory Sounds" OR "Bronchial Spasm" OR bronchospas* OR "Bronchial Hyperreactivity" OR "Respiratory Hypersensitivity" OR (bronch* AND (spasm* OR constrict*))) AND TITLE(exerc* OR train* OR fitness OR "physical activity" OR athlet* OR sport*) AND (diagnos* OR sensitiv* OR predictive OR accurac* OR specificity OR probability OR likelihood OR methacholine OR mannitol OR EVH OR screen* OR test*) AND LN(EN) Look for terms in: Citation and abstract Publication type: All publication types

Table B9. Therapy for EIB/EIA review – Cochrane Airways Register

Years/issue searched: 1900 to 2008 **Search date**: November 5, 2008 **Number of Results**: 1601
The following databases are searched systematically for the Cochrane Airways Register: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and hand searching of respiratory journals and meeting abstracts. (exerc* OR train* OR fitness OR physical OR athlete* OR sport*) AND (bronchoconstrict* OR asthma* OR antiasthma* OR wheez* OR "Respiratory Sounds" OR "Bronchial Spasm" OR bronchospas* OR "Bronchial Hyperreactivity" OR "Respiratory Hypersensitivity" OR (bronch* AND spasm*) OR (bronch* AND constrict*).OR (bronchial* OR respiratory OR airway* OR lung*) AND (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficiency)) OR EIB OR EIA

Table B10. Therapy for EIB/EIA review – ClinicalTrials.Gov: National Institutes of Health

Search date: November 28, 2008 **Number of Results**: 31
asthma OR eia OR eib OR exercise-induced

Table B11. Therapy for EIB/EIA review – ClinicalStudyResults.Org: PhRMA Clinical Study Results Database

Search date: November 28, 2008 **Number of Results**: 2
Browsed by trade and generic drug names

Appendix C. Forms

Inclusion Criteria Worksheet: Diagnosis of EIB/EIA review

Reviewer ID: **Date:** / /2009 **Record ID:**

Criteria	Yes	No	Unclear
1. ENGLISH LANGUAGE	☐	☐	
2. PUBLICATION TYPE			
a. Report of primary research	☐	☐	☐
3. STUDY OBJECTIVE			
a. Must be to diagnose or confirm diagnosis of EIB	☐	☐	☐
4. STUDY DESIGN			
a. Comparative study or…	☐	☐	☐
b. Single arm study (but results are compared to a previous standardized test (i.e. cannot just be a prevalence study)	☐	☐	☐
5. POPULATION			
a. >80% patients ≥6 years who are otherwise healthy (i.e., do not have bronchitis, COPD, cystic fibrosis, bronchiectasis, etc.) NOTE: participants may have asthma or suspected EIA/EIB	☐	☐	☐
6. INDEX TEST (circle the test)			
a. One of the following diagnostic tests: i. Self-reported history ii. Self-reported symptoms diary iii. Methacholine challenge iv. Sport or venue specific exercise challenges v. Eucapnic (or normocapnic) voluntary hyperpnea vi. Free running asthma screening test (FRAST) vii. Mannitol NOTE: if another testing method not listed above is used please flag as an 'other' below and keep separate from excluded pile	☐	☐	☐
7. REFERENCE STANDARD			
a. Standardized exercise challenge test (treadmill or Cycle ergometry) that resulted in a drop in $FEV_1 \geq 10\%$ from baseline	☐	☐	☐
8. OUTCOME			
a. Numeric data sufficient to create a 2 x 2 table and/or calculation of sensitivity, specificity, positive and negative likelihood ratios.	☐	☐	☐

Comments:

REVIEWER'S DECISION : Include ☐ **Exclude** ☐ **Unsure** ☐ **Other** ☐

FINAL DECISION: Include ☐ **Exclude** ☐ **Unsure** ☐
NOTE: To exclude must have said "NO" for at least one of 1-8.

Inclusion Criteria Worksheet: Therapy for EIB/EIA review

Reviewer ID: **Date:** / /2009 **Record ID:**

Criteria	Yes	No	Unclear
1. ENGLISH LANGUAGE	☐	☐	
2. PUBLICATION TYPE			
a. Report of primary research	☐	☐	☐
3. STUDY DESIGN			
a. Randomized controlled trial (parallel or cross-over)	☐	☐	☐
4. POPULATION			
a. >80% patients ≥6 years who are otherwise healthy (i.e., do not have bronchitis, COPD, cystic fibrosis, bronchiectisis)	☐	☐	☐
b. Confirmed diagnosis of EIB or EIA (defined as drop in FEV_1 or peak flow ≥10%) [EXCLUDE self-report diagnosis]	☐	☐	☐
5. INTERVENTION (circle the intervention)			
Q1. One of the following <u>regular dose therapies</u> for ≥1 week before a standard exercise challenge (focus - testing for tachyphylaxis) a. SABA (see separate list of SABA agents) b. LABA (formoterol or salmeterol)	☐	☐	☐
OR			
One of the following <u>single dose pre-exercise</u> therapies tested by standard exercise challenge	☐	☐	☐
Q2. Leukotriene receptor antagonists (LTRA) (montelukast or zafirlukast) Q3. Inhaled corticosteroid (ICS) (see separate list of ICS agents) Q4. Mast cell stabilizers (sodium cromoglycate or nedocromil) Q5. Anti-cholinergics (ipratropium, oxitropium, atropine)			
OR			
Q6. A 10-15 min warmup and/or cool down prior to a standard exercise challenge (focus: checking for the effect of a refractory period)	☐	☐	☐
6. COMPARATOR			
a. For SABA or LABA: placebo or any standard comparator treatments for ≥1 week	☐	☐	☐
OR			
For other therapies: A single dose of placebo or no treatment			
7. OUTCOME			
Study reports numeric data on at least one outcome of interest (e.g., max % fall FEV_1 from pre-exercise baseline, symptoms, presence/absence of EIA/EIB, % protection over placebo, recovery time, adverse effects).	☐	☐	☐

Comments:

REVIEWER'S DECISION : Include ☐ **Exclude** ☐ **Unsure** ☐

FINAL DECISION: Include ☐ **Exclude** ☐ **Unsure** ☐

NOTE: To exclude must have said "NO" for at least one of 1-7.

RELEVANT TO QUESTION(S):

☐ **1**. In patients with confirmed EIB/EIA, do patients using **SABA and/or LABA develop tachyphylaxis** to treatment and, if so, at what frequency compared to standard comparator treatments and/or placebo?

☐ **2 - 5**. In patients with confirmed EIA/EIB, does pre-exercise treatment with

2) leukotriene receptor antagonists (LTRA) therapy OR
3) mast cell stabilizers (sodium cromoglycate or nedocromil) therapy OR
4) inhaled corticosteroid (ICS) therapy OR
5) anti-cholinergics (ipratropium) therapy

reduce symptoms and prevent a ≥ 10% drop in FEV_1 compared to no treatment/placebo.

☐ **6**. In patients with confirmed EIA/EIB, does **a refractory period (10-15 min warmup and/or cool down**) reduce symptoms and prevent a ≥ 10% drop in FEV_1 compared to no treatment/placebo.

Data Extraction Form: Diagnosis of EIB/EIA review

I. CODER INFORMATION

1. Reviewer initials:	2. Time to extract (to nearest minute):
Applies to question: ☐1 self-reported hx/symptoms diary ☐2 methacholine challenge ☐3 sport/venue-specific exercise ☐4 eucapnic voluntary hyperpnea (EVH) ☐5 free running asthma screening test (FRAST) ☐6 mannitol	

II. PUBLICATION

3. Author:	4. Year of publication:	
5. Country trial conducted in (n=___ and complete list if >1): NR	6. Number of centres: single multi: n= NR	7. Publication Type: journal article industry reported trial abstract other (describe)
8. Funding Government Institution Industry (describe) No funding Other (describe) NR	9. Type of study: Trial Observational other (specify) _____	10. Design attributes prospective retrospective

III. STUDY CHARACTERISTICS

11. Study objective:	
12. Recruitment dates (mm/yy–mm/yy): NR	13. Source of participants: clinic/office school athletic team (sport/level) _____ other (describe) NR
14. No. of study days (i.e # screening/testing days)	15. No. of challenges per day
16. Time between challenges: 24 hours ≥2 days Other: _____ NR	
17. Inclusion criteria: NR	
18. Exclusion criteria: NR	
19. Definition of bronchial hyper reactivity (BHR) according to EVH or methacholine or mannitol (i.e. cut point for diagnosis): Report the reference or comments to support the cut point.	
20. Definition of EIA/EIB: ≥ 10% fall in FEV1 or PEF ≥ 15% fall in FEV1 or PEF ≥ 20 % fall in FEV1 or PEF Reproducible EIA/EIB (no definition given) Other (describe) e.g. self-report; physician diagnosed; symptoms etc. NR	
21. Please report the reference or comments made that supported the EIA/EIB definition they used (if any).	

IV. DIAGNOSTIC TESTS

Treadmill	
22. Duration of challenge:	6 minutes 8 minutes Other (describe) _____ NR
23. % of maximal heart rate / workload:	
24. Relative humidity:	≤50% Other (describe) _____ NR
25. Air temperature:	Air conditioned (ambient temp. 20-25˚ C) Other (describe) _____ NR
26. Referenced standardized protocol:	Yes No If yes, supply reference ID (if given): _____
27. Follow-up time points: (i.e. 1, 3, 5, 7, 30 min post challenge)	
Cycle ergometry	
28. Duration of challenge:	6 minutes 8 minutes Other (describe) _____ NR
29. % of maximal heart rate / workload:	
30. Relative humidity:	≤50% Other (describe) _____ NR
31. Air temperature:	Air conditioned (ambient temp. 20-25˚ C) Other (describe) _____ NR
32. Referenced standardized protocol:	Yes No If yes, supply reference ID (if given): _____
33. Follow-up time points: (i.e. 1, 3, 5, 7, 30 min post challenge)	
Self reported history/Questionnaire	
34. Summary of comments from study:	

Methacholine challenge	
35. Dosing protcol	**2 min tidal breathing method** ▪ 10 doubling concentrations of MCH (0.03, 0.06, 0.125, 0.25, 0.50, 1, 2, 4, 8, 16 mg/ml) ▪ Nebulizer using dry compressed air for power ▪ Perform baseline spirometry ▪ Noseclip should be worn ▪ Breathe quietly for 2 min. ▪ Measure FEV_1 30 – 90s after nebulization of each dose ▪ Commence subsequent concentrations with ≤5 min interval **5 breath dosimeter method** ▪ 5 quadrupling concentrations of MCH (0.0625, 0.25, 1,4,16 mg/ml) ▪ Perform baseline spirometry ▪ Noseclip should be worn ▪ Inhale slowly & deeply from nebulizer and exhale; repeat for 5 inhalations ▪ Measure FEV_1 30 – 90s after 5th inhalation ▪ Commence subsequent concentrations with ≤5 min interval **Other (specify)**
36. Follow-up time points: (i.e. 1, 3, 5, 7, 30 min post challenge)	

Sport/venue-specific exercise	
37. Sport:	
38. Venue:	
39. Duration:	
40. Follow-up time points: (i.e. 1, 3, 5, 7, 30 min post challenge)	
41. Other:	
EVH	
42. Description:	
FRAST	
43. Standard test:	YES NO If no, describe:
Mannitol	
44. Description:	
Resources used for diagnosis challenges	
45. Time:	
46. Personnel (who, how many?):	
47. Cost(s) (if given):	
48. Patient safety:	
49. Other (e.g. ease of administration):	

V. BASELINE CHARACTERISTICS (when possible report data post run-in/pre-test)

*Circle or describe units Indicate if no variance measure reported	
50. Age: years mean±SD; mean±SE; median (range); IQR	
51. Males: *n* (%)	
52. Ethnicity:	
53. Height:	
54. Weight:	
55. BMI:	
56. Number of participants enrolled/randomized: (n)	
57. Number of participants analyzed: (n)	
58. Number of dropouts/withdrawals: (n)	
59. Reasons for dropout/withdrawal:	
60. History of asthma/BHR:	YES NO NR If yes, how confirmed?
61. Proven EIA/EIB:	YES NO NR If yes, how confirmed?
62. Baseline severity of asthma: mild/mod/severe or stable (Report authors words) NR	
63. Index of activity/fitness level:	Sedentary (no activity per week) Normally active (1-3 days per week activity) Athletic (competitive athlete, 4+ days per week activity) Other NR
64. Atopic status: YES = to at least one allergen; NO=none were atopic Mix of atopy/no atopy (x%=yes; X%=no) (a positive skin prick test=atopic to at least 1)	
65. Baseline ICS history: NO = none on ICS YES = all on maintenance ICS mixed ICS use (x%= yes; X%= no) NR	
66. Which asthma medications were discontinued pre challenge and how long before challenge	
67. Baseline FEV1 (L): (mean±SD; mean±SE; median (range); IQR)	
68. Baseline FEV1 (% predicted): (mean±SD; mean±SE; median (range); IQR)	
69. Baseline PEF: (mean±SD; mean±SE; median (range); IQR)	
70. PC20 (mg/ml):	
71. Smoking Hx: never/past/current	

72. Other (describe)	

VI. REPORTED OUTCOMES

		Exercise Standard		Totals
		EIB (+)	EIB (-)	
Comparator 1	EIB (+)			
	EIB (-)			
Totals				

OTHER OUTCOMES REPORTED
73. Sensitivity:
74. Specificity:

VII. ADVERSE EVENTS/SIDE EFFECTS ☐ NR ☐ Statement re: no AE observed in study

	Exercise Standard	Comparator 1	Comparator 2	Comparator 3
Total reported				

ADDITIONAL COMMENTS

75.

Data Extraction Form: Therapy for EIB/EIA review

I. CODER INFORMATION

1. Reviewer initials:	2. Time to extract (to nearest minute):
3. Applies to question: ☐1 tachyphylaxis SABA or LABA ☐2 i [LTRA] ☐2 ii] [ICS ☐2 iii] [SCG / NCS ☐2 iv [anti-cholinergic] ☐6 refractory period	

II. PUBLICATION

4. Author:	5. Year of publication (last two digits):	
6. Country trial conducted in (n=___ and complete list if >1): NR	7. Number of centres: single multi: n= NR	8. Publication Type: journal article industry reported trial abstract other (describe)
9. Funding government institution Industry (describe) No funding other (describe) NR	10. Type of trial: parallel cross-over	11. Blinding open label single blind dble blind NR
12. Other design attributes double-dummy placebo-controlled		

III. STUDY CHARACTERISTICS

13. Recruitment dates (mm/yy–mm/yy): NR	14. Source of participants: clinic/office school athletic team other (describe) NR	
15. Run-in period? Yes NO [describe]		
16. No. of study days (i.e # screening/testing days)	17. No. of challenges per day	
18. Time between challenges: NR		
19. Exclusion criteria: NR		
20. Definition of EIA/EIB: ≥ 10% fall in FEV1 or PEF ≥ 15% fall in FEV1 or PEF ≥ 20 % fall in FEV1 or PEF Reproducible EIA/EIB (no definition given) Other (describe) e.g. self-report; physician diagnosed; symptoms etc. NR		
21. Please report the reference or comments made that supported the EIA/EIB definition they used (if any) we need to report this in a table for the funders.		
22. Exercise challenge: Inclined treadmill Bicycle ergometer FRAST (Free Running Asthma Screening Test) Sport-specific challenge Other (describe)	23. Duration of challenge 6 minutes 8 minutes Other (describe)	
24. Temperature Room/ambient temperature	25. Relative humidity	26. % of maximal heart rate / workload

Cold air Other (describe)		
27. Other conditions reported		

IV. TREATMENT GROUPS

	Group A	Group B	Group C	Group D	Total
28. Number of participants enrolled/randomized (*n*)					
29. Number of participants analyzed (*n*)					
30. Number of dropouts/withdrawals (*n*)					
31. Reasons for dropout/withdrawal					
INTERVENTIONS					
32. Drug 1: name					
33. Dose 1					
34. Delivery device 1: Diskhaler (diskus) pMDI (MDI) Turbuhaler Spinhaler Nebulizer Other (describe)					
35. Time 1: time med taken pre exercise (minutes)					
36. Drug 2: name					
37. Dose 2					
38. Delivery device 2: Diskhaler (diskus) pMDI (MDI) Turbuhaler Spinhaler Nebulizer Other (describe)					
39. Time 2: time med taken pre exercise (minutes)					
40. Current asthma medications allowed to continue during testing: YES NO					
41. Which asthma medications were allowed					
42. Which asthma medications were discontinued pre challenge and how long before challenge					

V. BASELINE CHARACTERISTICS (when possible report data post run-in/pre-treatment)

*Circle or describe units Indicate if no variance measure reported	Group A	Group B	Group C	Group D	Total
43. Age: years mean±SD;					

mean±SE; median (range); IQR					
44. Males *n* (%)					
45. Participants had confirmed asthma: YES NO					
46. Baseline severity of asthma: mild/mod/severe or stable (Report authors words later we will convert to GINA guideline category) NR					
47. Atopic status: YES = to at least one allergen; NO=none were atopic Mix of atopy/no atopy (x%=yes; X%=no) (a positive skin prick test=atopic to at least 1)					
48. Baseline ICS history: NO=none on ICS YES=all on maintenance ICS mixed ICS use (x%= yes; X%= no) NR					
49. Baseline FEV1: L					
50. Baseline FEV1 % predicted					
51. mea/max % fall FEV1 control / screening challenge mean±SD / SE; median(range); IQR					
52. Severity of EIB (mild/mod/severe)					
53. mean / max % fall PEF control / screening challenge mean±SD / SE; median(range); IQR					
54. Smoking Hx: never/past/current					
55. Other (describe)					

VI. REPORTED OUTCOMES (outcomes with data reported) circle or check outcome reported

56. Primary outcome:	
OTHER OUTCOMES REPORTED	
57. FEV1: L	58. Individual patient data
59. FEV1: Max % fall	60. Adverse events (I.e.) anaphylaxis. Had to d/c challenge etc.
61. FEV1: change	62. Side effects
63. FEV1: times measured	64. Time course of EIB (graph)
65. PEF: L/min	66. Repeat tests on same day
67. PEF: max % fall	68. Symptoms
69. PEF: change	70. Rescue medication use
71. PEF: times measured	72. Other (describe)
73. % protection	74. Other (describe)
75. Complete protection:	76. Other (describe)
77. Clinical protection	78. Other (describe)

VII. ADVERSE EVENTS/SIDE EFFECTS

	Group A	Group B	Group C	Group D	Total
Total reported					

VIII. CONCLUSIONS

Describe conclusions: (*Please, also describe such as: "Compared to B and C, A-----was-superior/inferior in ----", or "There were no differences between A and B in -----, but B was superior/inferior to C")*

ADDITIONAL COMMENTS

79.

Quality Assessment Form: Diagnosis of EIB/EIA review, QUADAS

1	The spectrum of patients was representative of the patients who would receive the test in practice.	YES	NO	UNCLEAR
2	Were selection criteria clearly defined?	YES	NO	UNCLEAR
3	Is the reference standard likely to classify the condition correctly? (Reference standard was specified as part of inclusion criteria)	YES	NO	UNCLEAR
4	Is the time period between reference standard and index test appropriate to be reasonably sure that the target condition did not change between the two tests?	YES	NO	UNCLEAR
5	Did the whole sample or a random selection of the sample, receive verification using a reference standard (partial verification bias)?	YES	NO	UNCLEAR
6	Did patients receive the same reference standard regardless of the index test results (differential verification bias)?	YES	NO	UNCLEAR
7	Was the execution of the index test described in sufficient detail to permit replication of the test?	YES	NO	UNCLEAR
8	Was the execution of the reference test described in sufficient detail to permit replication of the test?	YES	NO	UNCLEAR
9	Were the index test results interpreted without knowledge of the results of the reference standard?	YES	NO	UNCLEAR
10	Were the reference standard results interpreted without knowledge of the results of the index test?	YES	NO	UNCLEAR
11	Were the same clinical data available when index test results were interpreted as would be available when the test is used in practice? (Only applicable to self-reported history and self-reported symptoms diary)	YES	NO	UNCLEAR
12	Were uninterpretable/intermediate test results reported?	YES	NO	UNCLEAR
13	Were withdrawals from the study explained?	YES	NO	UNCLEAR

Guidelines for interpretation of QUADAS questions for EIB/EIA

1. *Was the spectrum of participants representative of the patients who would receive the test in practice?*
   Answer YES if
   - Unbiased recruitment methods: consecutively or randomly selected in a prospective way
   - Characteristics of participants are presented: Age, comorbidity (e.g., asthma), where they were recruited from (e.g., school, clinic, sport team, etc.), all have suspected EIB

   Answer NO if
   - Biased recruitment methods: volunteers, retrospective selection
   - Participants include those with confirmed (not suspected) EIB
   - Characteristics of participants are not reported

   Answer UNCLEAR if
   - There is not enough relevant information to score either a Yes or No.

2. *Were selection criteria clearly defined?*
   Answer YES if
   - There is information on how participants were selected for inclusion including recruitment methods and inclusion/exclusion criteria (e.g., age, EIB status, setting (i.e., high school), recruitment method)

   Answer NO if
   - There is no information regarding recruitment methods and inclusion/exclusion criteria

   Answer UNCLEAR if
   - There is not enough relevant information to score either a Yes or No.

3. *Is the reference standard likely to classify the condition correctly?*
   Answer YES
   - Standardized exercise challenge (treadmill or cycle ergometry) that resulted in a drop of ≥ 10% in FEV_1 as being acceptable.
   - Age-specific heart rate achieved during exercise (>80% of predicted)
   - Exercise duration ≥ 6 min

- Post exercise measure interval is approximately 2 min (i.e., 1, 3, 5, 7min)

Answer UNCLEAR if

- The achieved age-specific HR or exercise duration are not mentioned
- The achieved age-specific HR is mentioned but less than 80%
- The exercise duration is mentioned but less than 6 min
- Post exercise measure interval is longer than 2 min (i.e, 1, 4, 8m post exercise)

4. *Is the time period between reference standard and index test appropriate to be reasonably sure that the target condition did not change between the 2 tests?*

Answer YES if

- There was an acceptable delay between the 2 tests; doesn't apply to self report and a 2nd test (mark as NA where self report is the comparison test)
- We judged a time interval of at least 24 hours between tests as appropriate.

Answer NO if

- If the period between the 2 tests does not fall within the time interval

Answer UNCLEAR if

- There is not enough relevant information to score either a Yes or No.

5. *Did the whole sample or a random selection of the sample, receive verification using a reference standard (partial verification bias)?*

Answer YES if

- All participants received the reference test **before** receiving the index test; or
- In cases where the index test is given prior to the reference test, either all participants go on to receive the reference test or a random sample of participants receive the reference test

Answer NO if

- Less than 90% of the participants who received the index test also received the reference test and the selection of this smaller group is based on a non-random method (such as results from the index test)

Answer UNCLEAR if

- There is not enough relevant information to score either a Yes or No

6. *Did patients receive the same reference standard regardless of the index test results (differential verification)?*

Answer YES if

- All participants received the same reference test

Answer NO if

- Some participants received verification of EIB using a different reference standard or some of the participants who received the index test did not have their true disease state verified.

Answer UNCLEAR if

- There is not enough relevant information to score either a Yes or No

7. *Was the execution of the index test described in sufficient detail to permit replication of the test?*

Answer YES if …

- Details are provided about duration, dose, load, environmental conditions and other items relevant to the specific index test

Answer NO if

- There are no details about the execution of the index test.

Answer UNCLEAR if

- There is not enough relevant information to score either a Yes or No

8. *Was the reference standard described in sufficient detail to permit replication of the test?*
   Answer YES if
   - Information is reported on duration of challenge, % of maximal heart rate / workload, relative humidity, air temperature, or if a standardized protocol is referenced (i.e., AAS or similar).

   Answer NO if
   - There is no information about how the exercise challenge was conducted.

   Answer UNCLEAR if
   - There is not enough relevant information to score either a Yes or No

9. *Were the index test results interpreted without knowledge of the results of the reference standard?*

10. *Were the reference standard results interpreted without knowledge of the results of the index test?*
    Answer YES if
    - The authors stated explicitly that the results of the index test were interpreted blind to the results of the exercise challenge, and vice versa

    Answer NO if
    - If it does not seem likely that the test results were interpreted blind to the results of the other test

    Answer UNCLEAR if
    - It is not reported in the study

11. *Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?(**Applicable only** to Self reported history and Self reported symptoms diary)*
    Answer YES if
    - If the interpretation of the index test is fully automated and involves no interpretation
    - If the index test is interpreted with additional clinical data in the study, while these same clinical data will also be available when the index test is performed in practice
    - If the index test is interpreted without additional clinical data, and additional clinical data will also be unavailable when the index test is performed in practice

    Answer NO if
    - If the interpretation of the index test is not fully automated and involves interpretation components which can be influenced by additional clinical data
    - If the index test is interpreted with additional clinical data in the study, however, these clinical data will not be available when the index test is performed in practice
    - If the index test is interpreted without additional clinical data, however, additional clinical data will be available when the index test is performed in practice

    Answer UNCLEAR if
    - Not enough relevant information to score either a Yes or No

12. *Were uninterpretable/intermediate test results reported*?
    Answer YES if
    - It is clear that all test results are reported

    Answer NO if
    - You suspect that uninterpretable/indeterminate/intermediate results occur but are not reported

    Answer UNCLEAR if
    - There is no mention of whether such results occurred or how they were handled

13. *Were withdrawals from the study explained?*
    Answer YES if
    - All the participants enrolled are accounted for (i.e., a flow chart or description of reasons for dropouts or withdrawals)

    Answer NO if
    - Some participants did not receive both tests and are not accounted for

    Answer UNCLEAR if
    - It is not clear whether all participants who entered the study were accounted for

Note: We did not apply Item 7 (incorporation bias) from the original QUADAS tool as it does not apply to this review.

Quality Assessment Form: Therapy for EIB/EIA review (RCTs)

Jadad scale

	YES	NO
1. Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?	1	0
2. Was the study described as double-blind?	1	0
3. Was there a description of withdrawals and drop-outs?	1	0
4. Method to generate the sequence of randomization was described and was appropriate (e.g. table of random numbers, computer generated, coin tossing, etc.)	1	0
5. Method of double-blinding described and appropriate (identical placebo, active placebo, dummy)	1	0
6. Method of randomization described and it was **in**appropriate (allocated alternately, according to date of birth, hospital number, etc.)	-1	0
7. Method of double-blinding described but it was **in**appropriate (comparison of tablet vs. injection with no double dummy)	-1	0
OVERALL SCORE (Maximum 5)		

Concealment of treatment allocation – Schulz

Concealment of treatment allocation	☐ Adequate ☐ Inadequate ☐ Unclear

Adequate:	e.g. central randomization; numbered/coded containers; drugs prepared by pharmacy; serially numbered, opaque, sealed envelopes
Inadequate:	e.g. alternation, use of case record numbers, dates of birth or day of week; open lists
Unclear:	Allocation concealment approach not reported or fits neither above category

Appendix D. Excluded Studies

Diagnosis of EIB/EIA reviews

402 studies were excluded from the diagnostic test accuray reviews. Reasons for exclusion include: study design (n=116), population (n=8), no reference standard (n=21), no comparison (n=46), did not diagnose EIA/EIB (n=158), insufficient data (n=26), other diagnostic tests (n=24), duplicate publication (n=2), and language (n=1). In addition, we were unable to obtain copies of 10 studies.

Study Design (n = 116)

1. Bronchial asthma. Med Sport (Roma) 2006;59(1):25-42.
2. No perfect screening test for asthma. Sports Med Digest 1999;21(6):64-5.
3. Albers M, Schermer T, Van WC. Airflow limitation as a screening tool: too relevant to ignore, too conspicuous to apply? Chest 2005;128(4):1898-900.
4. Amirav I. Airway response to methacholine during exercise induced refractoriness in asthma. Thorax 1987;42(10):831.
5. Anderson SD, Argyros GJ, Magnussen H, Holzer K. Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. Br J Sports Med 2001;35(5):344-7.
6. Anderson SD, Silverman M, Tai E, Godfrey S. Specificity of exercise in exercise-induced asthma. Br Med J 1971;4(5790):814-5.
7. Anthonisen NR. Asthma questionnaires. Can Respir J 2007;14(2):77-8.
8. Ashbaugh SJ, Rubino I, Rose VL. At-risk athletes should be screened for exercise-induced asthma. Am Fam Physician 1998;57(2):332.
9. Barbosa e Silva O, Ribeiro Saraiva LC. Exercise test indications in children and adolescents. Rev Bras Med Esporte 2004;10(5):420-3.
10. Berglund E. Challenging an exercise challenge protocol [comment]. Eur Respir J 1994;7(10):1909.
11. Berman BA, Ross RN. Exercise-induced asthma. Cutis 1982;30(2):176.
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27. Colin A, Said E, Winter ST. Exercise-induced asthma in schoolchildren a pilot study in 2 Haifa districts Israel. Isr J Med Sci 1985;21(1):40-3.
28. Cotes JE, Reed JW. Recommendations on the use of exercise testing in clinical practice. Eur Respir J 2007;29(5):1064-6.

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30. D'Urzo AD. Hypercapnia during exercise in asthmatic subjects [comment]. J Appl Physiol 1995;78(1):372.

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Therapy for EIB/EIA review

368 studies were excluded from the review. Reasons for exclusion include: study design (n=60), population (n=32), intervention (n=214), no comparison (n=2), outcome (n=1), language (n=38), insufficient data (n=12), and duplicate publication (n=9). We were not able to retrieve the reports of 15 studies.

Study Design (n = 60)

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Duplicate Publication (n = 9)

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Appendix E. Studies Investigating Mast Cell Stabilizing Agents

The following 44 studies were included in three systematic reviews and two subsequent publications that investigated mast cell stabilizing agents.[72-75] Six of the studies in this list addressed one or more of the other key questions of this current report; they have been marked with an asterisk (*). Nine studies did not meet the inclusion criteria for this current report; most were excluded because they were not published in English or were not randomized controlled trials. These studies have been marked with a †.

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