FINAL REPORT

1999

EVIDENCE-BASED REVIEW

OF THE

AUSTRALIAN SIX STEP

ASTHMA MANAGEMENT PLAN

National Asthma Campaign

NSW HEALTH
Better Health Good Health Care

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NSW HEALTH DEPARTMENT

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EXECUTIVE SUMMARY

Background

The Australian Asthma Management Plan was published in 1989 and was the first of many international, consensus-based asthma guidelines. International and NHMRC standards are currently calling for guidelines to be refined using the principles of evidence-based medicine. There is also a growing demand from medical practitioners and consumers to have access to evidence-based recommendations for therapy. The National Asthma Campaign and New South Wales Health collaborated with the intention of pursuing this goal in 1996-1997. A steering committee of experts in asthma, epidemiology and health policy was established to guide an evidence-based review of the Australian Asthma Management Plan.

Beneficiaries

Groups in Australia that will benefit from this work include: health policy makers, guideline writers, researchers, consumers, general practitioners, respiratory physicians, students and educators.

Methods

The first stage of this work involved generating questions relevant to the Australian Asthma Management Plan recommendations, the development and conduct of literature searches and review of abstracts for relevance. Questions were categorised according to two criteria: the existence of high quality evidence to answer the question and, the clinical relevance of the recommendation. Questions which were considered to be both clinically important and for which randomised controlled trial data were available, were given the highest priority for review. Results from previously conducted systematic reviews were consulted to answer questions. If there were no relevant systematic reviews available, then a Cochrane systematic review or a critically appraised recommendation was commenced.

The Final Report

This is a comprehensive report of the available evidence supporting the Australian Asthma Management Plan. It has been created as a reference document for the Health Department. This report is complemented by a summary publication in the form of a pocket-sized reference, and a website version (see the NSW Health site: www.health.nsw.gov.au and the National Asthma Campaign site: www.NationalAsthma.org.au). These smaller publications

will evolve as systematic reviews replace critically appraised recommendations, and as the evidence base grows through of the publication of additional randomised controlled trials, and publication of new systematic reviews on the Cochrane Database of Systematic Reviews.

Achievements to Date

There are six steps of the Australian Asthma Management Plan. Five of these refer to the maintenance treatment of asthma and are the subject of the reviews. Evidence pertaining to Steps 5 and 6 has been collected and collated. Steps 2, 3 and 4 are in progress. The process has involved:

- The development and prioritisation of over 150 questions relevant to the Australian Asthma Management Plan.
- The assessment of over 2000 abstracts for relevance to the questions.
- The publication of five systematic reviews on the Cochrane Database of Systematic Reviews. (**see Cochrane Systematic Reviews**)
- Through collaboration with the Cochrane Airways Group, systematic reviews have been generated, based on questions developed by this working group. **(see Cochrane Systematic Reviews In Progress)**
- Twelve critically appraised recommendations have been conducted. **(see Critically Appraised Recommendations)**
- A set of clinically important questions identifying areas of asthma management where Level 1 or 2 evidence is not available and research is needed. **(see Research Questions)**

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AIMS

The primary aim of this project was to review the strength of current scientific evidence for the recommendations within the National Asthma Campaign's 1996 *Asthma Management Handbook.* The project aims to produce publications that allow for future expansion and development to reflect the changing status of the evidence.

This is a comprehensive report of the available evidence relating to specific questions derived from the six steps within the Australian Asthma Management Plan including:

- Assessment of Asthma Severity
- Achievement of Best Lung Function
- Maintenance of Best Lung Function (triggers and medications)
- Maintenance of Best Lung Function (optimising medication program)
- Use of Action Plans
- Patient Education and Review

BACKGROUND

The Australian Asthma Management Plan is published by the National Asthma Campaign (NAC). It provides guidance and recommendations for health professionals in the management of asthma according to a Six Step Plan and was the first publication of its kind[1]. Like many management plans which followed, the information contained in the Australian Asthma Management Plan was derived from consultation and consensus, but lacked direct reference to supporting evidence[2].

Recent years have seen the growth of evidence-based medicine and the international development of the Cochrane Collaboration. A decision was made to revise the Australian Asthma Management Plan using an evidence-based medicine approach in accordance with NHMRC guided principles in the *Development and Implementation of Clinical Practice Guidelines*[3].

An evidence-based approach to asthma management is a highly relevant tool for consumers of health care. People with asthma are faced with a bewildering array of therapy choices and strategies to avoid asthma triggers, including both conventional and alternative approaches.

Consumers express strong preferences to learn more about asthma[4] and should have access to Level 1 Evidence to help inform their decisions.

This review of evidence and production of a companion publication that summarises the availability and strength of the evidence, will:

- Ensure the appropriateness of asthma management guidelines,
- Facilitate improved management of asthma, leading to lower health costs, and
- Reinforce the leading edge of Australian health-policy makers on the world stage, clarifying areas for future research in asthma and its clinical management.

NAC SIX STEP ASTHMA MANAGEMENT PLAN

Step 1 ***Assess Asthma Severity***[5]

- Assess overall severity when the patient is stable, not during an acute attack.

Step 2 ***Achieve Best Lung Function***

- Treat with intensive asthma therapy until the 'best' lung function is achieved.
- Back titrate to the lowest dose that maintains good symptom control and best lung function.

Step 3 ***Maintain Best Lung Function: Identify and Avoid Trigger Factors***

- Identify and avoid trigger factors and inappropriate medication.

Step 4 ***Maintain Best Lung Function: Optimise Medication Program***

- Treat with the least number of medications and use the minimum doses necessary.
- Ensure the patient understands the difference between 'preventer', 'reliever' and 'symptom controller' medications.
- Take active steps to reduce the risk of adverse effects from medication.

Step 5 ***Develop an Action Plan***

- Discuss and write an individualised plan for the management of exacerbations.
- Detail the increases in medication doses and include when and how to gain rapid access to medical care.

Step 6 ***Educate and Review Regularly***

- Ensure patients and their families understand the disease, the rationale for their treatment and how to implement their Action Plan.
- Emphasise the need for regular review, even when asthma is well controlled.

LEVELS OF EVIDENCE

The initial focus of this report was to establish the availability of published evidence and the extent to which recommendations were supported by Level 1 and 2 Evidence. The New South Wales Department of Health (NSW Health) has published the following definitions for grading evidence[6]:

Level 1 Systematic review of randomised controlled trials / large multi-centre randomised trial

Level 2 One or more randomised controlled trials

Level 3 Controlled trials without randomisation; cohort, case-control, analytic studies; multiple time series, before and after studies (preferably from more than one centre or research group)

Level 4 Other observational studies

Level 5 Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

METHODS

Cochrane Collaboration Airways Group

Strong links were established with the Cochrane Collaboration Airways Group, situated in St George's Hospital, London, which has conducted searches of its database for systematic reviews and randomised trials. The Cochrane Airways Group Database consists of randomised controlled trials and controlled clinical trials pertaining to airways disease derived from an amalgamation of Medline, Embase, Central Index of Nursing and Allied Health Literature (CINAHL) and handsearching of journals and abstracts. It is the most comprehensive single source of evidence for airways disease available in the world.

Steering Committee:

Chair

- **Dr Christine Jenkins**, *Chairman, National Asthma Campaign; respiratory physician, Sydney, NSW*

- **Members**

Ms Nicola Atkin, *Project Officer, Centre for Research and Clinical Policy, NSW Health*

Associate Professor Paul Glasziou, *Social and Preventative Medicine, School of Medicine, University of Queensland, Herston, QLD*

Dr Peter Gibson, *Member, NAC Education Committee; Staff Specialist, Respiratory Medicine, John Hunter Hospital, Newcastle, NSW; Australasian Editor, Cochrane Airways Group*

Professor Richard Henry, *Member, NAC Evaluation Committee; Head of School of Paediatrics, University of New South Wales, Sydney, NSW*

Professor Michael Hensley, *Professor and Head of Medicine, Newcastle University Medical School; Director, Respiratory Medicine, John Hunter Hospital, Newcastle, NSW*

Dr Jeannine Liddle, *Manager, Centre for Clinical Policy and Practice, NSW Health (to 1998)*

Associate Professor Charles Mitchell, *Chair, NAC Evaluation Committee; Chair of Medicine, Princess Alexandra Hospital, Brisbane, QLD*

Dr Isabella Smith, *Acting Manager, Centre for Research and Clinical Policy, NSW Health*

Ms Kristine Whorlow, Chief Executive Officer, National Asthma Campaign

- **Project Officers**

Ms Jennifer Coughlan, *Research Project Manager, Department of Respiratory Medicine, John Hunter Hospital, NSW; Reviewer, Cochrane Airways Group*

Ms Amanda Wilson, *Project Officer, Department of Respiratory Medicine, John Hunter Hospital, NSW; Reviewer, Cochrane Airways Group*

Establishment of the Steering Committee

In 1997-1999, NSW Health provided funding to the National Asthma Campaign for a review of the evidence supporting recommendations made in the *Asthma Management Handbook*[7].

The National Asthma Campaign brought together a group with expertise in asthma, systematic reviews, statistics, including a member of the original team that published the 1989 version of the Australian Asthma Management Plan. A full-time project officer was appointed to coordinate the project.

Contributors

Content experts responded to requests by the Steering Committee to participate in the review process. These people included: John Anderson, Petr Bremner, Russell Vandenberg, Ian Yang, Anita Chalmers, Linda Seeto, R Baker, Genevieve Gabb, Agnes Vitry, Emily Stone, K Hui, Allen Isles, Gary Russell, Margaret Curran, Helen Reddel, Gary Baker, Susan Sawyer, Felicity Finlayson, Peter Middleton, Smita Shah, Simon Bowler, Frank Thien, Carolyn Bakin, Richard Douglass, Bill Musk, Richard Wood-Baker.

Available Resources

Resources employed for this project included the expertise of the working party, the existing Australian Asthma Management Plan and physical resources including space, office facilities and computing facilities provided by the Department of Respiratory Medicine, John Hunter Hospital and the Discipline of Medicine, Newcastle University Medical School.

Generation of Questions

The generation of clinically relevant questions pertaining to the recommendations within the Australian Asthma Management Plan was achieved in the first year of project. Each member of the expert panel was allocated a 'Step' for which they were responsible for the clarification and refinement of questions. Once the questions were individually clarified, they were sent back to the project officer who conducted searches documenting the search strategy and the number of citations this yielded. These data were then presented to the group, which prioritised and further refined the questions. Where necessary, search strategies were refined to improve sensitivity.

The questions were categorised according to two criteria:

1. Clinical importance, and
2. Availability of relevant randomised controlled trials.

Questions of high clinical importance with available randomised controlled trials were addressed as a high priority.

Synthesis of the Literature

Two approaches to synthesising the literature were adopted:

1. Critically appraised recommendations
2. Cochrane systematic reviews

Critically Appraised Recommendations

Critically appraised recommendations (CAR) were devised by the working party, as a specific instrument to synthesize the literature. A critically appraised recommendation is a comparative summary of all the randomised controlled trials which relate to a clinical question derived from a recommendation in the *Asthma Management Handbook*. The critically appraised recommendations used in this report were completed according to a standardised protocol (Appendix I). When a Cochrane systematic review was not possible, or not available, a critically appraised recommendation has been used to answer questions. Critically appraised recommendations are not seen as adequate substitutes for Cochrane systematic reviews, however they provide a rudimentary synthesis of current literature and are considered an effective use of limited time and resources. An example of a CAR is shown in Appendix II.

Cochrane Systematic Reviews and Meta-analyses

A Cochrane systematic review is a comprehensive, systematic, qualitative and quantitative analysis of randomised trials. Systematic reviews are superior to critically appraised recommendations as they provide quantitative estimations of effect size, attempt to identify all available trials in any language and use methods that minimise bias.

Project staff have completed five Cochrane systematic reviews. Through collaboration with the Cochrane Airways Group, a further seven systematic reviews based on the questions formulated, have been completed. These reviews make a significant contribution to providing evidence-based based answers to questions in Steps 3, 4, 5 and 6.

This report presents a combination of the critically appraised recommendations and systematic reviews conducted in order to optimise the use of limited resources and funding. An example of a recommendation addressed by both a critical appraisal and a subsequent Cochrane systematic review, is attached (Appendix II).

PRESENTATIONS

- The methodology and progress of this project were presented to senior members of the Thoracic Society of Australia and New Zealand for comment at the 1998 meeting in Adelaide.
- Thoracic Society of Australia and New Zealand 1998 - Cochrane Session. Six systematic reviews were presented.
- Thoracic Society of Australia and New Zealand 1999 meeting in Canberra - Cochrane Session. Six systematic reviews were presented.

THE FINAL REPORT

Target Audience

This report is intended for use by the following groups:

- Those responsible for the implementation of guidelines for clinical practice.
- Those responsible for making and implementing policy decisions with regards to public health.
- Those responsible for making and implementing health economic decisions.

Other Beneficiaries

A large number of other groups will benefit from this project. These include:

- Researchers who will have access to a summary of research opportunities;
- Medical practitioners and consumers who will be able to validate their level of confidence in the recommendations;
- Educators and students in the health sciences.

SUMMARY OF PROJECT ACHIEVEMENTS

- The development of 150 questions pertinent to recommendations in the Australian Asthma Management Plan.
- The assessment of over 2000 published randomised controlled trial abstracts to answer these questions.
- The publication of five completed reviews on the Cochrane Database of Systematic Reviews (refs 8-12).

- Abstracts accepted for presentation at the 1999 Thoracic Society of Australia and New Zealand meeting.
- Completion of the evidence-based review of Steps 5 and 6.
- Substantial progress with Steps 2, 3 and 4.

RESULTS

The results of the evidence-based review processes are presented for each Step in the Asthma Management Plan in separate sections. There are two additional sections: The Diagnosis of Asthma, and Acute Asthma. Each section is divided into four components:

1) Cochrane Systematic Reviews – this section provides the abstracts of all pertinent completed reviews.
2) Critically Appraised Recommendations – this section identifies the appropriate *Asthma Management Handbook* recommendation, the question/s arising from that recommendation, a summary of the randomised controlled trials (usually in table format), an answer to the question, and any limitations and comments.
3) Cochrane Systematic Reviews in Progress – this section lists the titles of Cochrane Protocols and Titles of systematic reviews currently not completed but in progress.
4) Research Questions – this section lists the questions that have been derived from recommendations in the *Asthma Management Handbook* for which no randomised controlled trials or meta-analyses are available.

ACKNOWLEDGEMENTS

We would like to thank Steve Milan, Anna Bara and Jane Dennis of the St George's Cochrane Airways Group, London, whose valuable assistance and knowledge have made this report possible.

DIAGNOSIS OF ASTHMA

No Level 1 evidence was identified to support the recommendations in this heading. The recommendation for the assessment of asthma severity reflects consensus and current clinical practice. The review found no randomised controlled trials or meta-analyses on questions related to these recommendations. It is known that data exist in the form of non-randomised studies (i.e. levels 3 and 4) but these were not searched for as part of the review. Many of the questions related to this heading are suitable for future research.

Cochrane Systematic Reviews

No Cochrane Systematic Reviews have been conducted on this topic.

Critically Appraised Recommendations

No Critically Appraised Recommendations have been conducted on this topic.

Cochrane Systematic Reviews in Progress

There are no Cochrane Systematic Reviews in progress.

Research Questions

1 Can adult/childhood asthma be sub-grouped into different types according to the natural history? (e.g. symptoms and lung function / average lung function)
2 If asthma can be sub-grouped, do the various subgroups have different prognoses and responses to treatment?
3 What is the sensitivity and specificity of a diagnosis made by a FEV_1 bronchodilator response of 15%?
4 What is the effect of a doctor's diagnosis of asthma on episodic respiratory symptoms?
5 What is the effect of a doctor's diagnosis of asthma on future management of asthma?
6 What is the effect of a doctor's diagnosis of asthma on prognosis?

STEP 1: ASSESS ASTHMA SEVERITY

No Level 1 evidence was identified to support the recommendations in this step. The recommendation for the assessment of asthma severity reflects consensus and current clinical practice. The review found no randomised controlled trials or meta-analyses on questions related to Step 1 recommendations. It is known that data exist in the form of non-randomised studies (i.e. levels 3 and 4) but these were not searched for as part of the review. Many of the questions related to Step 1 are suitable for future research.

Cochrane Systematic Reviews

No Cochrane Systematic Reviews have been conducted on this topic.

Critically Appraised Recommendations

No Critically Appraised Recommendations have been conducted on this topic.

Cochrane Systematic Reviews in Progress

There are no Cochrane Systematic Reviews in progress.

Research Questions

1 Is measuring asthma severity necessary?
2 What is the relationship between lung function and symptom severity? (eg in mild asthma)
3 Is there a difference between intensity and frequency of symptoms in the assessment of asthma severity?
4 Is there a role for regular preventer medications for patients who have infrequent episodic asthma?
5 Does individualising treatment on the basis of severity lead to better outcomes?
6 Does assessing the severity of every patient and individualising treatment improve health outcomes?
7 What is the outcome for patients assessed and managed as high risk?
8 Does the assessment of asthma severity influence choice of therapy?
9 Does the assessment of asthma severity influence intensity of therapy?
10 Does the assessment of asthma severity influence outcome of therapy?
11 Does the assessment of asthma severity influence maintenance therapy requirements?
12 Does the presence of nocturnal asthma correlate with objective measures of asthma?
13 What is the sensitivity / specificity of work loss / missed school as markers of severity?

STEP 2: ACHIEVE BEST LUNG FUNCTION

Cochrane Systematic Reviews

No Cochrane Systematic Reviews have been conducted on this topic.

Critically Appraised Recommendations

1 Inhaled steroid therapy in adults

1.1 In patients with an FEV_1 of greater than 80%, does treatment with an inhaled corticosteroid ≤ 800µg/day plus beta-agonists as required achieve best lung function?

1.2 In patients with an FEV_1 of less than 80% predicted, does treatment with an inhaled corticosteroid ≤ 800µg/day plus beta -agonists as required achieve best lung function?

1.3 Does treatment with an inhaled corticosteroid ≤ 800µg/day plus beta-agonists as required have a beneficial effect on clinical assessments of mild-moderate persistent asthma achieve best lung function?

1.4 In patients with an FEV_1 of greater than 80% does treatment with an inhaled corticosteroid >800µg/day plus beta-agonists as required achieve best lung function?

1.5 In patients with an FEV_1 of less than 80% predicted, does treatment with an inhaled corticosteroid > 800µg/day plus beta-agonists as required achieve best lung function?

1.6 Does treatment with an inhaled corticosteroid > 800µg/day plus beta-agonists as required have a beneficial effect on clinical assessments of mild-moderate persistent asthma?

2 What is the effect of an inhaled corticosteroid on airflow obstruction and airway inflammation in children with asthma not responsive to sodium cromoglycate?

Cochrane Systematic Reviews in Progress

There are no Cochrane Systematic Reviews in progress on this topic.

Research Questions

Thirty research questions have been identified for this step.

Critically Appraised Recommendations

1 Inhaled Steroid Therapy In Adults

Treatment recommendations for inhaled steroids in Step 2 of the *Asthma Management Handbook* are based on FEV_1. Questions were developed to reflect the wording of the actual recommendations.

The *Asthma Management Handbook* recommendation states:
'If FEV_1 is less than 80% predicted reading or if the initial measurement increases by at least 15% after bronchodilator medication, intensive therapy to reduce airway inflammation and reverse airway obstruction is recommended.

A suitable treatment regimen for adults with mild-moderate persistent asthma is an inhaled corticosteroid (750/800 µg/day) plus beta-agonist when required.

For those with more severe manifestations at presentation, a higher dose of inhaled steroid (750/800-2000 µg/day) and/or oral corticosteroids may be required.'

The abstracts retrieved by a search of the Cochrane Controlled Trials Register using the terms 'asthma' OR 'wheez*' AND 'inhaled corticoster*' OR 'beclometh*' OR 'triamcin*' OR 'flutic*' OR 'budes*' OR 'betameth*', were downloaded electronically into a database. Each abstract was read and characteristics of baseline FEV_1, asthma status (chronic or acute), intervention type and outcomes were recorded in separate fields. The full text version of the papers was retrieved if the study was a randomised controlled trial comparing an inhaled corticosteroid with a placebo in adults. These papers were divided into six groups based on the dose of inhaled corticosteroid and baseline FEV_1 to reflect the recommendation (see table below).

	Baseline FEV_1 > 80% predicted	**Baseline FEV_1 ≤ 80% predicted**	**Baseline FEV_1 % predicted not specified**
ICS dose ≤800 µg /day	**Question 1**	**Question 2**	**Question 3**
ICS dose >800 µg /day*	**Question 4**	**Question 5**	**Question 6**

**Fluticasone propionate studies were included in these reviews if the daily dose multiplied by two was greater than 800µg.*

Study design, intervention and outcome data were extracted and recorded on standardised data extraction sheets by two assessors. Data were compared and a table of the results collated.

The following critically appraised recommendations are the result.

STEP 2: Adult Steroid Series – Question 1.1:

	Baseline FEV_1 > 80% predicted	**Baseline FEV_1 ≤ 80% predicted**	**Baseline FEV_1, % predicted not specified**
ICS dose ≤800µg/day	**Question 1**	**Question 2**	**Question 3**
ICS dose >800µg/day	**Question 4**	**Question 5**	**Question 6**

The shaded box represents the FEV_1 and steroid dose characteristics of the studies included in this appraisal.

RECOMMENDATION: *If FEV_1 is less than 80%, or if the initial measurement increases by at least 15% after bronchodilator medication, intensive therapy to reduce airway inflammation and reverse airway obstruction is recommended. A suitable treatment regimen for adults with mild-moderate persistent asthma is an inhaled corticosteroid (750/800µg/day) plus beta-agonist when required.*

Question: In patients with an FEV_1 of greater than 80%, does treatment with an inhaled corticosteroid ≤ 800µg/day plus beta-agonists as required:

- improve lung function, asthma symptoms, use of rescue medication, nocturnal waking, assessment of efficacy or bronchial hyperresponsiveness?
- affect inflammatory markers such as blood eosinophils or serum/sputum eosinophil cationic protein?
- increase plasma cortisol? and/or
- increase patient-related adverse events?

Answer: Inhaled corticosteroids ≤ 800µg/day consistently improved PEF and bronchial hyperresponsiveness. There was inconsistent improvement in symptoms and the use of rescue medications. Little effect was reported on FEV_1 and there was no effect noted in the number of exacerbations or adverse events.

Search Strategy: The Cochrane Controlled Trials Register (CENTRAL) was searched using the terms 'asthma' OR 'wheez*' AND 'inhaled corticoster*' or 'beclometh*' or 'triamcin*' or 'flutic*' or 'budes*' or 'betameth*'.

Methods: 674 abstracts were reviewed and the full text version of a paper was obtained if the trial compared an inhaled corticosteroid with a placebo in adults. Ninety-six papers were reviewed and included if they reported a double-blind randomised parallel or crossover trial of an inhaled corticosteroid ≤ 800µg per day in adult patients with mild asthma ($FEV_1 \geq 80\%$).

Results: Five trials reporting five interventions of two different inhaled corticosteroids over a period from 1985 to 1997 met the inclusion criteria. (See Table 1.)

Comments/Limitations: The treatment periods ranged from four to twelve months. There were only three studies that reported FEV_1. No studies reported night waking or plasma cortisol. Serum ECP was reported in one study and blood eosinophils in two.

References:

1 Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. American Review Of Respiratory Disease 1990; 142:832-6.

2 Kraan J, Koeter GH, v.d. Mark TW, Sluiter HJ, de Vries K. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. Journal Of Allergy And Clinical Immunology 1985; 76:628-36.

3 Osterman K, Carlholm M, Ekelund J, Kiviloog J, Nikander K, Nilholm L, Salomonsson P, Strand V, Venge P, Zetterstrom O. Effect of 1 year daily treatment with 400 micrograms budesonide (Pulmicort Turbuhaler) in newly diagnosed asthmatics. European Respiratory Journal 1997; 10:2210-5.

4 Prieto L, Berto JM, Gutierrez V, Tornero C. Effect of inhaled budesonide on seasonal changes in sensitivity and maximal response to methacholine in pollen-sensitive asthmatic subjects. European Respiratory Journal 1994; 7:1845-51.

5 Ryan G, Latimer KM, Juniper EF, Roberts RS, Hargreave FE. Effect of beclomethasone dipropionate on bronchial responsiveness to histamine in controlled nonsteroid-dependent asthma. Journal Of Allergy And Clinical Immunology 1985; 75:25-30.

Prepared by:

1. Jennifer Coughlan 21 December, 1998
2. Amanda Wilson 21 December, 1998

Table 1. Summary of Studies: Question 1.1 (FEV_1>80% predicted, ICS≤800μg/day): Effect of inhaled corticosteroids on asthma outcomes

Trial	N	Drug	Daily dose (μg)	Rx Duration	Baseline FEV_1	FEV_1	PEF	Symptoms	Rescue Meds	Night Waking	BHR	Exacerbations	Plasma Cortisol	AEs	Serum ECP	Blood Eosin
Kraan (1985)	17	BUD	100 qid	4 wks	85%	Sig	Sig	Sig	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Sig
Juniper (1990)	29	BUD	200 am 200 pm	12 month	91%	Not sig	Not stated	Sig	Sig	Not stated	Sig	Not stated	Not stated	Not sig	Not stated	Not stated
Prieto (1994)	28	BUD	800 dly	5 months	102%	Not stated	Not stated	Not stated	Not stated	Not stated	Sig	Not sig	Not stated	Not stated	Not stated	Not stated
Osterman (1997)	62	BUD	200 bd	12 month	91%	Not stated	Sig	Not sig	Not sig	Not stated	Sig	Not stated	Not stated	Not stated	Not sig	Not sig
Ryan (1985)	10	BDP	400 dly	4 wks	>70%	Not sig	Not stated	Not stated	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated

TAA = triamcinolone acetonide; FP = fluticasone proprionate; BV = betamethasone valerate; BDP = beclomethasone; BUD = budesonide; sig = significant difference; not sig = no significant difference.

STEP 2: Adult Steroid Series – Question 1.2:

	Baseline FEV_1 > 80% predicted	**Baseline FEV_1 ≤ 80% predicted**	**Baseline FEV_1 % predicted not specified**
ICS dose ≤800µg /day	**Question 1**	**Question 2**	**Question 3**
ICS dose >800µg /day	**Question 4**	**Question 5**	**Question 6**

The shaded box represents the FEV_1 and steroid dose characteristics of the studies included in this appraisal

RECOMMENDATION: *If FEV_1 is less than 80% or if the initial measurement increases by at least 15% after bronchodilator medication, intensive therapy to reduce airway inflammation and reverse airway obstruction is recommended. A suitable treatment regimen for adults with mild-moderate persistent asthma is an inhaled corticosteroid (750/800µg /day) plus beta-agonist when required.*

Question: In patients with an FEV_1 of less than 80% predicted, does treatment with an inhaled corticosteroid ≤ 800µg/day plus beta-agonists as required:

- improve lung function, asthma symptoms, use of rescue medication, nocturnal waking, assessment of efficacy or bronchial hyperresponsiveness?
- affect inflammatory markers such as blood eosinophils or serum/sputum eosinophil cationic protein?
- increase plasma cortisol? and /or
- increase patient-related adverse events?

Answer: An inhaled corticosteroid ≤ 800µg/day improved FEV_1, PEF, asthma symptoms, use of rescue medication, nocturnal waking and doctor assessed efficacy. There was no significant change in plasma cortisol levels. Adverse events were assessed in six trials. One trial reported a significant increase in adverse events.

Search Strategy: The Cochrane Controlled Trials Register (CENTRAL) was searched using the terms 'asthma' OR 'wheez*' AND 'inhaled corticoster*' or 'beclometh*' or 'triamcin*' or 'flutic*' or 'budes*' or 'betameth*'.

Methods: 657 abstracts were reviewed and the full text version of the paper was obtained if the trial compared an inhaled corticosteroid with a placebo in adults. Ninety-six papers were reviewed and included if they were a double-blinded randomised parallel or crossover trial of an inhaled corticosteroid ≤ 800µg per day used in adults with moderate to severe asthma ($FEV_1 \leq 80\%$).

Results: Eight trials reporting 12 interventions of four different inhaled corticosteroids over a period from 1974 to 1997, met the inclusion criteria (see Table 2).

Comments/Limitations: The results appear to be more consistently positive among more recent studies. These studies generally had larger sample sizes and longer treatment periods. The recent studies also were more consistent in their definition of asthma and clearly defined inclusion criteria.

References:

1 Holst PE, O'Donnell TV. A controlled trial of beclomethasone dipropionate in asthma. New Zealand Medical Journal 1974; 79:769-73.

2 Lawrence M, Wolfe J, Webb DR, Chervinsky P, Kellerman D, Schaumberg JP, Shah T. Efficacy of inhaled fluticasone propionate in asthma results from topical and not from systemic activity. Am J Respir Crit Care Med 1997; 156:744-51.

3 McAllen MK, Kochanowski SJ, Shaw KM. Steroid aerosols in asthma: an assessment of betamethasone valerate and a 12-month study of patients on maintenance treatment. Br Med J 1974; 1:171-5.

4 Molema J, van Herwaarden CL, Folgering HT. Effects of inhaled budesonide on the relationships between symptoms, lung function indices and airway hyperresponsiveness in patients with allergic asthma. Pulmonary Pharmacology 1989; 1:179-85.

5 Pearlman DS, Noonan MJ, Tashkin DP, Goldstein MF, Hamedani AG, Kellerman DJ, Schaberg A. Comparative efficacy and safety of twice-daily fluticasone propionate powder versus placebo in the treatment of moderate asthma. Ann Allergy Asthma Immunol 1997; 78:356-62.

6 Sheffer AL, LaForce C, Chervinsky P, Pearlman D, Schaberg A, Brown L, DeBoisblane BP, Donohue JF, George RB, Grossman J, Kelsen SG, McCain KF, Metzger WJ, Pleskow W, Sahn S, Schoenwetter W, Selner JC, Vandewalker ML, Winder J. Fluticasone propionate aerosol: Efficacy in patients with mild to moderate asthma. Journal of Family Practice 1996; 42:369-375.

7 Wasserman SI, Gross GN, Schoenwetter WF, Munk ZM, Kral KM, Schaberg A, Kellerman DJ. A 12-week dose-ranging study of fluticasone propionate powder in the treatment of asthma. Journal of Asthma 1996; 33:265-74.

8 Wolfe JD, Selner JC, Mendelson LM, Hampel FJ, Schaberg A. Effectiveness of fluticasone propionate in patients with moderate asthma: A dose-ranging study. Clinical Therapeutics 1996; 18:635-646.

Prepared by:

1. Jennifer Coughlan 21 December, 1998
2. Amanda Wilson 21 December, 1998

Table 2: Question 1.2 (FEV_1<80% predicted, ICS≤800μg/day): Effect of inhaled corticosteroids on asthma outcomes

Trial	N	Drug	Daily Dose	Rx Duration	BL FEV_1	FEV_1	PEF	Symptoms	Rescue Meds	Night Waking	BHR	Dr Efficacy	Plasma Cortisol	AEs	Serum ECP	Blood Eosin
Wolfe (1996)	304	FP	200	12 wks	65%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not stated	Not sig	Not stated	Not stated
Pearlman (1997)	342	FP	100	12 wks	56%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not sig	Not sig	Not stated	Not stated
Pearlman (1997)	342	FP	200	12 wks	66.5 %	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not sig	Not sig	Not stated	Not stated
Lawrence (1997)	127	FP	200	6 wks	66%	Sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Not sig	Not sig	Not stated	Not stated
Sheffer (1996)	149	FP	50	12 wks	63%	Sig	not sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated
Sheffer (1996)	152	FP	100	12 wks	63%	Sig	Sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Sig	Not stated	Not stated
Sheffer (1996)	152	FP	200	12 wks	63%	Sig	Sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Sig	Not stated	Not stated
Wasserman (1996)	256	FP	100	12 wks	50 - 80%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not sig	Not sig	Not stated	Not stated
Wasserman (1996)	256	FP	200	12 wks	50 - 80%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not sig	Not sig	Not stated	Not stated
McAllen (1977)	18	BV	800	4 wks	10/18 had FEV_1 < 50%	Not stated	Sig	Sig	Sig	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated	Not stated
Holst (1974)	9	BDP	400	6 weeks	66%	Not sig	Not stated	Not sig	Not sig	Not sig	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Molema (1989)	14	BUD	400	6 wks	68%	Sig	Sig	Sig	Sig	Not sig	Sig	Not stated	Not stated	Not stated	Not stated	Not stated

TAA=triamcinolone acetonide; FP=fluticasone proprionate;BV=betamethasone valerate;BDP=beclomethasone;BUD=budesonide;sig=significant difference;not sig=no significant difference.

STEP 2: Adult Steroid Series – Question 1.3:

	Baseline FEV_1 >80% predicted	**Baseline FEV_1 ≤80% predicted**	**Baseline FEV_1 % predicted not specified**
ICS dose ≤800µg/day	**Question 1**	**Question 2**	**Question 3**
ICS dose >800µg/day	**Question 4**	**Question 5**	**Question 6**

The shaded box represents the FEV_1 and steroid dose characteristics of the studies included in this appraisal.

RECOMMENDATION: *If FEV_1 is less than 80% or if the initial measurement increases by at least 15% after bronchodilator medication, intensive therapy to reduce airway inflammation and reverse airway obstruction is recommended. A suitable treatment regimen for adults with mild-moderate persistent asthma is an inhaled corticosteroid (750/800µg /day) plus beta-agonist when required.*

Question: Does treatment with an inhaled corticosteroid ≤ 800µg/day plus beta-agonists as required have a beneficial effect on clinical assessments of mild-moderate persistent asthma?
The following outcomes were assessed:

- lung function
- asthma symptoms
- use of rescue medication
- nocturnal waking
- bronchial hyperresponsiveness
- plasma cortisol
- doctor assessment of efficacy of drugs
- adverse events.

Answer: An inhaled corticosteroid ≤800µg/day improved FEV_1, PEF, symptoms, nocturnal waking, bronchial hyperresponsiveness and doctor assessed efficacy. There were no significant differences in plasma cortisol levels or adverse events. Use of rescue medication improved in nine of the 16 interventions that measured this outcome.

Search Strategy: The Cochrane Controlled Trials Register (CENTRAL) was searched using the terms 'asthma' OR 'wheez*' AND 'inhaled corticoster*' or 'beclometh*' or 'triamcin*' or 'flutic*' or 'budes*' or 'betameth*'.

Methods: 657 abstracts were reviewed and the full text version of the paper was obtained if the trial compared an inhaled corticosteroid with a placebo in adults. Ninety six papers were reviewed and included if they were a double-blinded randomised parallel or crossover trial of an inhaled corticosteroid ≤800µg per day used in adults with asthma (FEV_1 not specified as being above or below 80% predicted).

Results: Eleven trials reporting 18 interventions of five inhaled corticosteroids over a period from 1973 to 1997 met the inclusion criteria (see Table 3).

Comments/Limitations: Results appear to be more consistently positive among the more recent studies. These studies generally had larger sample sizes and longer treatment periods. The more recent studies also were more consistent in their definition of asthma and had clearly defined inclusion criteria. In the studies included on the basis of ≥15% reversibility

and where baseline FEV_1 was not stated, improvement in FEV_1 was less likely to be significantly improved. This could be due to the baseline FEV_1 being > 80% predicted.

References:

1 Chervinsky P, van As A, Bronsky EA, Dockhorn R, Noonan M, LaForce C, Pleskow W. Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. The Fluticasone Propionate Asthma Study Group [see comments]. Journal Of Allergy And Clinical Immunology 1994; 94:676-83.

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Prepared by:

1. Jennifer Coughlan 21 December, 1998
2. Amanda Wilson 21 December, 1998

Table 3: Question 1.3 (FEV_1 not specified, ICS≤800μg/day): Effect of inhaled corticosteroids on asthma outcomes

Trial	N	Drug	Daily Dose	Rx Duration	BL FEV_1	FEV_1	PEF	Symptoms	Rescue Meds	Night Waking	BHR	Dr Efficacy	Plasma Cortisol	AEs	Serum ECP	Blood Eosin
Welch (1997)	114	TAA	200	6 wks	2.44 l/minmean	Sig	Sig	Sig	Not sig	Not stated	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated
Welch (1997)	115	TAA	400	6 wks	2.51l/min mean	Sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated
Chervinsky (1994)	238	FP	50	8 wks	PEF 80%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not stated	Not sig	Not stated	Not stated
Chervinsky (1994)	238	FP	200	8 wks	PEF 80%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not stated	Not sig	Not stated	Not stated
Hartley (1977)	18	BV	800	4 wks	PEF fall ≥15%	Not stated	Not stated	Not stated	Not stated	Not stated	EIA sig	Not stated	Not stated	Not stated	Not stated	Not stated
Riordan (1974)	25	BV	800	2 wks	PEF rev ≥15%	Not sig	Sig	Sig	Not sig	Not stated	Not stated	Not stated	Not sig	Not sig	Not stated	Not stated
Riordan (1974)	25	BDP	400	2 wks	PEF rev ≥15%	Not sig	Sig	Sig	Not sig	Not stated	Not stated	Not stated	Not sig	Not sig	Not stated	Not stated
Gaddie (1973)	15	BDP	400	2 wks	0.69 mean	Sig	Not stated	Not stated	Not sig	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated	Not stated
Kivity (1994)	34	BUD	800	8 wks	Diurn var >15%	Sig	Sig	Not sig	Not sig	Not stated	Not sig	Not stated	Not stated	Not sig	Not stated	Not stated
Lorentzen (1990)	103	BUD	200	6 wks	PEF 80%	Not stated	Not sig	Not sig	Sig	Sig	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated
Lorentzen (1990)	103	BUD	400	6 wks	PEF 80%	Not stated	Sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Nor sig	Not stated	Not stated
Wong (1994)	37	BUD	800	2-4 wks	>15% rev	Sig	Not stated	Not stated	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
Jones (1994)	265	BUD	400 am	12 wks	PEF 80%	Not stated	Sig	Not sig	Not sig	Not sig	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated
Jones (1994)	265	BUD	400 pm	12 wks	PEF 80%	Not stated	Sig	Not sig	Not sig	Not sig	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated
Jones (1994)	265	BUD	200am 200pm	12 wks	PEF 80%	Not stated	Sig	Sig	Sig pm	Sig	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated
Wongtim (1995)	20	BUD	400 bd	8 wks	Rev >15%	Not stated	Not stated	Sig	Sig	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
O'Byrne (1996)	40	BUD	200 bd	4 month	"mild"	Not stated	Sig	Sig	Sig	Not stated	Not stated	Not sig	Not stated	Not sig	Not stated	Not stated
O'Byrne (1996)	37	BUD	400 bd	4 month	"mild"	Not stated	Sig	Sig	Sig	Not stated	Not stated	Not sig	Not stated	Not sig	Not stated	Not stated

TAA=triamcinolone acetonide; FP=fluticasone proprionate;BV=betamethasone valerate;BDP=beclomethasone;BUD=budesonide;sig=significant difference;not sig=no significant difference; EIA=exercise induced asthma.

STEP 2: Adult Steroid Series – Question 1.4:

	Baseline FEV_1 >80% predicted	**Baseline FEV_1 ≤80% predicted**	**Baseline FEV_1 % predicted not specified**
ICS dose ≤800µg /day	**Question 1**	**Question 2**	**Question 3**
ICS dose >800µg /day	**Question 4**	**Question 5**	**Question 6**

The shaded box represents the FEV_1 and steroid dose characteristics of the studies included in this appraisal.

RECOMMENDATION: *If FEV_1 is less than 80% or if the initial measurement increases by at least 15% after bronchodilator medication, intensive therapy to reduce airway inflammation and reverse airway obstruction is recommended. A suitable treatment regimen for adults with mild-moderate persistent asthma is an inhaled corticosteroid (750/800µg /day) plus beta-agonist when required.*

Question: In patients with an FEV_1 of greater than 80% does treatment with an inhaled corticosteroid >800µg/day plus beta-agonists as required:

- improve lung function, asthma symptoms, use of rescue medication, nocturnal waking, assessment of efficacy or bronchial hyperresponsiveness?
- affect inflammatory markers such as blood eosinophils or serum/sputum eosinophil cationic protein?
- increase plasma cortisol? and/or
- increase patient-related adverse events?

Answer: An inhaled corticosteroid > 800 µg/day consistently improved peak expiratory flow and bronchial hyperresponsiveness. There was improvement reported in FEV_1, symptoms and use of rescue medication. Nocturnal waking improved in one study.

Search Strategy: The Cochrane Controlled Trials Register (CENTRAL) was searched using the terms 'asthma' OR 'wheez*' AND 'inhaled corticoster*' or 'beclometh*' or 'triamcin*' or 'flutic*' or 'budes*' or 'betameth*'.

Methods: 674 abstracts were reviewed and the full text version of the paper was obtained if the trial compared an inhaled corticosteroid with a placebo in an adult population. The full text versions of 96 papers were reviewed and included if they reported a double-blind randomised parallel or crossover trial of an inhaled corticosteroid > 800µg per day in adults with mild asthma (FEV_1 ≥80%).

Results: Fourteen trials (reported in 17 papers) using 14 interventions of four different inhaled corticosteroids, from 1990 to 1997, met the inclusion criteria (see Table 4).

Comments/Limitations: The treatment periods ranged from 4 days to 5 months. Despite a high baseline FEV_1 (mean of all studies was 90%) 6 of 10 studies reported a significant improvement in FEV_1 and 10 of 13 studies reported a significant reduction in bronchial hyperresponsiveness. There was inadequate data to allow comment on doctor-assessed efficacy, plasma cortisol, adverse events, and serum eosinophilic cationic protein or blood eosinophils. Trigg et al reported highly significant differences in bronchial mucosal

eosinophilia, however there were no significant differences in bronchial alveoli lavage eosinophil counts. Vanthenen et al noted a significant reduction in exercise-induced bronchial hyperresponsiveness. Olivieri et al saw a significant decrease in mucosal eosinophils and mast cells.

References:

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Prepared by:

1.	Jennifer Coughlan	21 December, 1998
2.	Amanda Wilson	21 December, 1998

Table 4: Question 1.4 (FEV_1>80% predicted, ICS >800μg/day): Effect of inhaled corticosteroids on asthma outcomes

Trial	N	Drug	Daily Dose (μg)	Rx Duration	BL FEV_1	FEV_1	PEF	Symptoms	Rescue Meds	Night Waking	BHR	Dr Efficacy	Plasma Cortisol	AEs	Serum ECP	Blood Eosin
Zu Wallack (1990)	37	TAA	1200	6 wks	85%	Sig	Not sig	Not stated	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
Carpentiere (1990)	16	BDP	1000	4 wks	82%	Sig	Not stated	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated	Not stated	Not stated	Not stated
Trigg (1994)	23	BDP	1000	4 months	85%	Not sig	Not stated	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated	Not stated	Not stated	Not stated
Vatrella (1996)	20	BDP	1000	5 months	90%	Not sig	Sig	Sig	Sig	Not stated	Sig	Not stated	Not stated	Not stated	Sig	Sig
Fuller (1991)	10	BUD	1200	3 wks	90%	Not sig	Sig	Not sig	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
Kharitonov (1996)	11	BUD	1600	3 wks	91%	Not sig	Not stated	Not stated	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
Yates (1996)	12	BUD	1600	2 wks	91%	Sig	Sig	Sig	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
Vanthenen (1991)	40	BUD	1600	6 wks	95%	Sig	Sig	Sig	Sig	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
O'Connor (1992)	12	BUD	1600	2 wks	96%	Not stated	Not stated	Not stated	Not stated	Not stated	Sig	Not stated	Not stated	Not sig	Not stated	Not stated
Booms (1997)	30	BUD	1600	12 wk	89%	Not stated	Not stated	Not stated	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
Burke (1996)	16	BUD	1600	6 wks	94%	Sig	Sig	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated	Not stated	Not stated	Sig
Clark (1997)	10	BUD	2000	4 days	89%	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Sig	Not stated	Not stated	Not stated
Olivieri (1997)	17	FP	500	6 wks	104%	Not stated	Not stated	Not stated	Not stated	Not stated	Sig	Not stated	Not stated	Not stated	Not stated	Not stated
Overbeek (1996)	31	FP	1000	12 wks	85%	Sig	Not stated	Sig	Not stated	Sig	Sig	Not stated	Not stated	Not stated	Not stated	Not stated

TAA=triamcinolone acetonide; FP=fluticasone proprionate;BV=betamethasone valerate;BDP=beclomethasone;BUD=budesonide;sig=significant difference;not sig=no significant difference.

STEP 2: Adult Steroid Series – Question 1.5:

	Baseline FEV_1 > 80% predicted	**Baseline FEV_1 ≤ 80% predicted**	**Baseline FEV_1 % predicted not specified**
ICS dose ≤800µg /day	**Question 1**	**Question 2**	**Question 3**
ICS dose >800µg /day	**Question 4**	**Question 5**	**Question 6**

The shaded box represents the FEV_1 and steroid dose characteristics of the studies included in this appraisal.

RECOMMENDATION: *If FEV_1 is less than 80% or if the initial measurement increases by at least 15% after bronchodilator medication, intensive therapy to reduce airway inflammation and reverse airway obstruction is recommended. A suitable treatment regimen for adults with mild-moderate persistent asthma is an inhaled corticosteroid (750/800µg /day) plus beta-agonist when required.*

Question: In patients with an FEV_1 of less than 80% predicted, does treatment with an inhaled corticosteroid > 800µg/day plus beta-agonists as required:

- improve lung function, asthma symptoms, use of rescue medication, nocturnal waking, assessment of efficacy or bronchial hyperresponsiveness?
- affect inflammatory markers such as blood eosinophils or serum/sputum eosinophil cationic protein?
- increase plasma cortisol? and/or
- increase patient-related adverse events?

Answer: An inhaled corticosteroid >800µg/day consistently improved FEV_1, peak expiratory flow, asthma symptoms, use of rescue medication, nocturnal waking and doctor assessed efficacy. None of the included studies measured bronchial hyperresponsiveness. There was no significant increase in plasma cortisol levels or adverse events.

Search Strategy: The Cochrane Controlled Trials Register (CENTRAL) was searched using the terms 'asthma' OR 'wheez*' AND 'inhaled corticoster*' or 'beclometh*' or 'triamcin*' or 'flutic*' or 'budes*' or 'betameth*'.

Methods: 674 abstracts were reviewed and the full text version of the paper was obtained if the trial compared an inhaled corticosteroid with a placebo in adults. Ninety-six papers were reviewed and included if they reported a double-blind randomised parallel or crossover trial of an inhaled corticosteroid > 800 µg per day in patients with moderate to severe asthma (FEV_1 ≤80)

Results: Six trials reporting seven interventions of three different inhaled corticosteroids over a period from 1982 to 1998 met the inclusion criteria. (See Table 5.)

Comments/Limitations: The treatment periods ranged from 5 to 12 weeks. None of the studies measured bronchial hyperreactivity. Fluticasone propionate studies were included in this review if the daily dose multiplied by two was greater than 800µg.

References:

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Prepared by:

1. Jennifer Coughlan & Amanda Wilson 21 December, 1998
2. Dr Genevieve Gabb 05 July, 1998

Table 5: Question 1.5 ($FEV_1 \leq 80\%$ predicted, ICS >800μg/day): Effect of inhaled corticosteroids on asthma outcomes

Trial	N	Drug	Daily Dose (μg)	Rx Duration	BL FEV_1	FEV_1	PEF	Symptoms	Rescue Meds	Night Waking	BHR	Dr Efficacy	Plasma Cortisol	AEs	Serum ECP	Blood Eosin
Bernstein (1982)	90	TAA	1600	6 wks	20-80%	Sig	Not stated	Sig	Not stated	Sig	Not stated	Sig	Not sig	Not sig	Not stated	Not stated
Wasserman (1996)	256	FP	500	12 wks	50-80%	Sig	Sig	Not sig	Sig	Sig	Not stated	Sig	Not sig	Not sig	Not stated	Not stated
Wolfe (1996)	130	FP	500	12 wks	65%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not stated	Not sig	Not stated	Not stated
Wolfe (1996)	128	FP	1000	12 wks	65%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not stated	Not sig	Not stated	Not stated
Lawrence (1997)	142	FP	1000	6 wks	65%	Sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Not sig	Not sig	Not stated	Not stated
Brannan (1998)	64	BDP	1000	5 wks	50-75%	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not sig	Not sig	Not stated	Not stated
Salmeron (1989)	43	BDP	1500	8 wks	53%	Sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated

TAA=triamcinolone acetonide; FP=fluticasone proprionate;BV=betamethasone valerate;BDP=beclomethasone;BUD=budesonide;sig=significant difference;not sig=no significant difference.

STEP 2: Adult Steroid Series – Question 1.6:

	Baseline FEV_1 > 80% predicted	**Baseline FEV_1 ≤ 80% predicted**	**Baseline FEV_1 % predicted not specified**
ICS dose ≤800 µg /day	**Question 1**	**Question 2**	**Question 3**
ICS dose > 800 µg /day	**Question 4**	**Question 5**	**Question 6**

The shaded box represents the FEV_1 and steroid dose characteristics of the studies included in this appraisal.

RECOMMENDATION: *If FEV_1 is less than 80% or if the initial measurement increases by at least 15% after bronchodilator medication, intensive therapy to reduce airway inflammation and reverse airway obstruction is recommended. A suitable treatment regimen for adults with mild-moderate persistent asthma is an inhaled corticosteroid (750/800µg /day) plus beta-agonist when required.*

Question: Does treatment with an inhaled corticosteroid > 800µg/day plus beta-agonists as required have a beneficial effect on clinical assessments of mild-moderate persistent asthma? The following outcomes were assessed:

- improve lung function, asthma symptoms, use of rescue medication, nocturnal waking, assessment of efficacy or bronchial hyperresponsiveness;
- affect inflammatory markers such as blood eosinophils or serum/sputum eosinophil cationic protein;
- increase plasma cortisol, and/or
- increase patient-related adverse events?

Answer: An inhaled corticosteroid >800µg/day improved FEV_1, peak expiratory flow, symptoms, use of rescue medication, nocturnal waking and doctor assessed efficacy. None of the included studies measured bronchial hyperresponsiveness. Only one study measured inflammatory markers showing a significant reduction in eosinophilic cationic protein and a non-significant reduction in blood eosinophils. There was no significant increase in plasma cortisol levels. Inhaled corticosteroids did not cause a significantly higher number of adverse events over placebo treatment.

Search Strategy: The Cochrane Controlled Trials Register (CENTRAL) was searched using the terms 'asthma' OR 'wheez*' AND 'inhaled corticoster*' or 'beclometh*' or 'triamcin*' or 'flutic*' or 'budes*' or 'betameth*'.

Methods: 674 abstracts were reviewed and the full text version of the paper was obtained if the trial compared an inhaled corticosteroid with a placebo in adults. The full text versions of 96 papers were reviewed and included if they reported a double-blind randomised parallel or crossover trial of an inhaled corticosteroid >800µg per day in patients with moderate to severe asthma (FEV_1 ≥80% predicted).

Results: Three trials reporting three interventions of three different inhaled corticosteroids, from 1989 to 1997 met the inclusion criteria (see Table 6).

Comments/Limitations: The treatment periods ranged from 4 to 8 weeks. None of the studies measured bronchial hyperreactivity. Fluticasone propionate studies were included in this review if the daily dose multiplied by 2 was greater than 800µg.

References:

1 Chervinsky P, van As A, Bronsky EA, Dockhorn R, Noonan M, LaForce C, Pleskow W. Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. J Allergy Clin Immunol 1994; 94:676-83.

2 Venge P, Dahl R. Are blood eosinophil number and activity important for the development of the late asthmatic reaction after allergen challenge? Eur Respir J 1989;2 Suppl.6:430s-434s.

3 Welch MJ, Levy S, Smith JA, Feiss G, Farrar JR. Dose-ranging study of the clinical efficacy of twice-daily triamcinolone acetonide inhalation aerosol in moderately severe asthma. Chest 1997; 112:597-606.

Prepared by:

1. Jennifer Coughlan 21 December, 1998
2. Amanda Wilson 21 December, 1998

Table 6: Question 1.6 (FEV_1 not specified, ICS >800μg/day): Effect of inhaled corticosteroids on asthma outcomes

Trial	N	Drug	Daily Dose (μg)	Rx Duration	BL FEV_1	FEV_1	PEF	Symptoms	Rescue Meds	Night Waking	BHR	Dr Efficacy	Plasma Cortisol	AEs	Serum ECP	Blood Eosin
Welch (1997)	115	TAA	1600	6 wks	2.52 mean	Sig	Sig	Sig	Sig	Not stated	Not stated	Not stated	Not stated	Not sig	Not stated	Not stated
Chervinsky (1994)	159	FP	1000	8 wks	PEF 80%	Sig	Sig	Sig	Sig	Sig	Not stated	Sig	Not stated	Not sig	Not stated	Not stated
Venge (1989)	13	BUD	1000	4 wks	>15% rev	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Sig	Not sig

TAA=triamcinolone acetonide; FP=fluticasone proprionate;BV=betamethasone valerate;BDP=beclomethasone;BUD=budesonide;sig=significant difference;not sig=no significant difference.

2 Inhaled corticosteroids in children non-responsive to sodium cromoglycate

Recommendation: In children with frequent episodic asthma, inhaled corticosteroids should be used if sodium cromoglycate or nedocrimol sodium are ineffective.

Question: What is the effect of an inhaled corticosteroid on airflow obstruction and airway inflammation in children with asthma not responsive to sodium cromoglycate?

Answer: Level II evidence from a single small randomised controlled trial supports the recommendation to introduce inhaled corticosteroids in paediatric subjects not responsive to sodium cromoglycate.

Search strategy: The Cochrane controlled trials register (CENTRAL) was searched using the terms 'asthm*' or 'wheez*' AND 'inhaled corticoster*' or 'budes*' or 'flutic*' or 'beclometh*' or 'triamcin*' AND 'cromogly*'.
The search was extended by checking the reference lists of the articles selected, and also the relevant pharmaceutical companies.

Methods*:* The initial Cochrane search found 13 abstracts, which were reviewed. The full text version of the paper was obtained if the trial compared an inhaled corticosteroid with cromoglycate in children. An additional 4 trials were identified from reference lists. No additional trials were identified from pharmaceutical companies. The full text of 11 papers were reviewed and were included if they were a double-blind randomised parallel or crossover trial of an inhaled corticosteroid in children not controlled on sodium cromoglycate.

Results: 10 trials were excluded because they did not demonstrate that subjects were uncontrolled on sodium cromoglycate. The single included trial (see table 1) demonstrated that betamethasone valerate compared with sodium cromoglycate produced significant improvements in symptoms and morning and evening peak expiratory flow. Non-significant improvements in lung function and clinic peak expiratory flow were also reported. No additional benefit was reported when betamethasone valerate and sodium cromoglycate were combined.

Comments/ Limitations*:* The included trial was small and did not adequately define statistical methodology, the timing of withdrawals or the number of subjects contributing to the final analysis.

References:

1. Hiller E, Milner A. Betamethasone 17 valerate aerosol and disodium cromoglycate in severe childhood asthma. Brit J Dis Chest 1975; 69:103-106.

Prepared by:

1 Carolyn Dakin 8 May, 1999
2 Jennifer Coughlan 14 May, 1999

Cochrane Systematic Reviews in Progress

There are no Cochrane Systematic Reviews in progress on this topic.

Research Questions

1 Does improving lung function result in better health outcomes?
2 If aggressive initial treatment with inhaled steroids does not improve asthma control or achieve normal lung function does this mean that the diagnosis is wrong?
3 If aggressive initial treatment with inhaled steroids does not improve asthma control or achieve normal lung function, if the diagnosis is right, is the prognosis poor?
4 If aggressive initial treatment with inhaled steroids does not improve asthma control or achieve normal lung function and the diagnosis is right, will future management be difficult?
5 Do adults who have regular office spirometry have better health outcomes?
6 Do children who have regular medical review have better health outcomes?
7 Do children who regularly measure symptoms have better health outcomes?
8 Is there a correlation between office and home measurement of lung function?
9 Does the regular use of an electronic diary spirometer improve health outcomes?
10 How should best lung function be achieved?
11 Is best lung function achieved more often and/or more quickly in subjects with severe asthma by the use of inhaled corticosteroids (750-2000µg daily) or oral corticosteroids?
12 Is asthma control and symptom relief achieved more often and/or more rapidly in children with infrequent episodic asthma by the use of sodium cromoglycate, nedocromil sodium or inhaled corticosteroids?
13 Is asthma control/ symptom relief achieved more often and/or more rapidly in children with frequent episodic asthma by the use of sodium cromoglycate, nedocromil sodium or inhaled corticosteroids?
14 Is asthma control/ symptom relief achieved more often and/or more rapidly in children with persistent episodic asthma by the use of sodium cromoglycate, nedocromil sodium or inhaled corticosteroids?
15 Does sodium cromoglycate reduce airflow obstruction and/or airway inflammation in children with asthma?
16 Does nedocromil sodium reduce airflow obstruction and/or airway inflammation in children with asthma?
17 Do inhaled corticosteroids reduce airflow obstruction and/or airway inflammation in children with asthma?
18 Do inhaled corticosteroids reduce airflow obstruction and/or airway inflammation in children not responsive to sodium cromoglycate?
19 Do inhaled corticosteroids reduce airflow obstruction and/or airway inflammation in children not responsive to nedocromil sodium?
20 Does specialist review help to achieve best lung function in adults with asthma unresponsive to inhaled corticosteroids less than 800µg daily?
21 Does specialist review help to achieve best lung function in adults with asthma unresponsive to inhaled corticosteroids greater than 800µg daily?
22 Does specialist review help to achieve best lung function in adults with asthma unresponsive to inhaled corticosteroids greater than 800µg daily plus an oral corticosteroid?
23 Does specialist review reduce airflow obstruction and/or airway inflammation in

children with asthma not responsive to sodium cromoglycate?

24 Does specialist review reduce airflow obstruction and/or airway inflammation in children with asthma not responsive to nedocromil sodium?

25 Does regular lung function measurement of clinic FEV_1 reverse airflow obstruction in adults with asthma?

26 Does regular lung function measurement by PEF diary reverse airflow obstruction in adults with asthma?

27 Does regular lung function measurement by FEV_1 diary reverse airflow obstruction in adults with asthma?

28 Does regular lung function measurement by clinic FEV_1 reverse airflow obstruction in children with asthma?

29 Does regular lung function measurement by PEF diary reverse airflow obstruction in children with asthma?

30 Does regular lung function measurement by FEV_1 diary reverse airflow obstruction in children with asthma?

STEP 3: MAINTAIN BEST LUNG FUNCTION AND IDENTIFY AND AVOID TRIGGER FACTORS

Cochrane Systematic Reviews

1 House dust mite control measures for asthma
2 Reflux and asthma
3 Allergen immunotherapy for asthma
4 Caffeine for asthma
5 Nedocromil sodium for preventing exercise-induced bronchoconstriction
6 Influenza vaccination in asthma: efficacy and side-effects

Critically Appraised Recommendations

1 SO_2 , exercise exposure and lung function in asthma
2 NO_2 exposure in combination with exercise
3 NO_2 in combination with SO_2
4 NO_2 at rest
5 Antibiotic use during exacerbations of asthma
6 Allergen avoidance and asthma

Critically Appraised Recommendations in Progress

1 Does exposure to cold air increase asthma severity/ exacerbations?

Cochrane Systematic Reviews in Progress

1 Allergen responsiveness of asthmatics and its association with exposure to nitrogen dioxide
2 Dietary avoidance of cow's milk protein for preventing asthma in children
3 Dietary marine fatty acids for asthma
4 Tartrazine exclusion for allergic asthma
5 Does high salt intake increase the severity of asthma?
6 What is the efficacy of vitamin C supplementation in the treatment of asthma
7 Does exposure to environmental tobacco smoke increase asthma severity / exacerbations?
8 What is the effect of influenza vaccination on asthma?

Cochrane Systematic Reviews in Progress

1 Does exposure to cold air increase asthma severity/ exacerbations?

Research Questions

Twenty-three research questions have been identified for this step.

Cochrane Systematic Reviews

1 *HOUSE DUST MITE CONTROL MEASURES FOR ASTHMA*

Hammarquist C, Burr ML, Gotzsche PC.
Date of most recent substantive amendment: 30/04/1998.

Abstract

Objectives: The primary objective of this review was to determine whether mite-sensitive asthmatics benefit from measures designed to reduce their exposure to house dust mite antigen in the home. A secondary objective was to determine whether mite-sensitive asthmatics benefit from a proven reduction of exposure to house dust mite antigen.

Search strategy: Trials potentially eligible were obtained through searches in the databases 'Asthma and Wheez* databases' set up by the Cochrane Airways Group. The databases contain records downloaded from three systems: CINAHL (The Cumulative Index to Nursing & Allied Health Literature), Medline and Embase. CINAHL goes back to 1982, Medline to 1966 and Embase to 1980. The search was run across all fields in the database and picked up records with mite* in the title, abstract or keyword (descriptor) fields. The identification of RCTs was made searching on [random* OR trial* OR placebo OR double-blind OR double blind OR single-blind OR single blind OR comparative study OR controlled study] in all fields. There was no restriction by language. The bibliography of each paper was checked for additional references. Primary authors of RCTs were contacted, when necessary, for clarification. Handsearches of Respiration 1980 to 1996 (CH) and Clinical and Experimental Allergy 1980 to 1996 (MB) were made.

Selection criteria: Only randomised trials were included. The participants were diagnosed as having bronchial asthma by a physician. Their mite sensitisation was assessed by skin testing, bronchial provocation tests or serum assay for IgE antibodies. The following outcomes were considered: subjective well-being; asthma symptom scores; medication usage; days of sick leave from school/work; number of unscheduled visits to a physician/hospital; FEV_1 (forced expiratory volume in one second); PEFR (peak expiratory flow rate); PC20 (provocative concentration that causes a 20% fall in FEV_1); skin prick testing.

Data collection and analysis: Two of the authors independently selected the trials for inclusion and extracted the data, any ambiguities were resolved by discussion. Ninety-five per cent confidence intervals (CI) were calculated. If $p<0.10$ for the test of heterogeneity, a random effects analysis was carried out. For continuous data, the standardised mean difference was used, since data were sometimes presented on different scales.

Main results: We did not find convincing evidence among the studies we reviewed that control measures to reduce the exposure to mites or their products improved the patients' asthma. The total number of patients who improved after the experimental interventions was very similar to the corresponding number in the control groups (41/113 versus 38/117, odds ratio 1.20, 95% CI 0.66 to 2.18). Asthma symptom scores were grossly heterogeneous ($p <0.0001$ for test of heterogeneity), but there was no indication of an effect; the standardised

mean difference was -0.06 (95% CI -0.54 to 0.41). No significant difference was noted overall for medication usage; the standardised mean difference was only -0.14 (95% CI -0.43 to 0.15).

Peak flow in the morning was the most commonly reported variable. The standardised mean difference was -0.03 (95% CI -0.25 to 0.19). For chemical methods there was a significant difference which, however, favoured the control group, the standardised mean difference was -0.50 (95% CI -0.98 to -0.01) (this study had a baseline difference which favoured the control group). For physical methods the difference was 0.06 (95% CI -0.26 to 0.37) for the five cross-over studies and 0.33 (95% CI -0.28 to 0.94) for the only group comparative trial. For combination methods the difference was 0.02 (95% CI -0.46 to 0.50). There was no effect on FEV_1, the standardised mean difference was 0.09 (95% CI -0.16 to 0.33).

There was no difference between the treatments for PC20; the standardised mean difference was -0.04 (95% CI -0.32 to 0.23).

One study reported that none of the twelve subjects missed school during treatment, as opposed to three during the control period. There was, however, no mention of reasons for missing school. None of the studies reported on number of unscheduled visits to a physician/hospital or results of skin prick testing after the treatment.

Conclusions: Current chemical and physical methods aimed at reducing exposure to house dust mite allergens seem to be ineffective and cannot be recommended as prophylaxis for mite-sensitive asthmatics.

Citation: Hammarquist C, Burr ML, Gotzsche PC. House dust mite control measures for asthma (Cochrane Review). In: The Cochrane Library, Issue 1,1999. Oxford: Update Software.

2 ***REFLUX AND ASTHMA***

Gibson PG, Coughlan, JL, Henry RL.
Date of most recent substantive amendment: 12/02/99.

Abstract

Objectives: The objective of this systematic review was to evaluate the effectiveness of treatment of gastro-oesophageal reflux in adults and children with asthma, in terms of its benefit on asthma.

Search Strategy: The Cochrane Airways Group database was searched using the terms: 'asthma' AND 'gastro-oesophageal reflux' OR 'gastroesophageal reflux' OR 'gastro-esophageal reflux' OR 'reflux' OR 'ger' OR 'gerd' OR 'acid' OR 'esophagus' AND 'cimetidine' OR 'ranitidine' OR 'famotidine' OR 'nizatidine' OR 'omeprazole' OR 'pantoprazole' OR 'lansoprazole' OR 'surgery' OR 'Nissen'.

Selection Criteria: Studies were included if they met the following criteria:
1) The study design was a randomised controlled trial;
2) The intervention was a treatment for oesophageal reflux;
3) The subjects had a diagnosis of both asthma and gastro-oesophageal reflux;
4) The study reported asthma health outcomes.

Data Collection and Analysis: The Cochrane Airways Group database was searched using the above search strategy. Two independent reviewers reviewed abstracts and the full text version of all potential studies was retrieved. Two reviewers independently assessed these for inclusion. Agreement was measured and disagreements resolved by discussion. Assessment of study quality, documentation of study characteristics and interventions and extraction of outcome data were conducted independently by two reviewers and inconsistencies resolved by returning to the full text version of the paper or by contacting the authors. Data were analysed using the usual Cochrane methods provided in the RevMan meta-analysis package. Dichotomous data were assessed using the Mantel-Haenszel relative risk or risk reduction methods (Greenland 1985). A weighted mean difference using the methods described in Sinclaire et al (1992) was used for continuous data. All analysis used the random effects models described in Der Simmonian and Laird (1986).

Main Results: The search yielded 17 potentially relevant randomised controlled trials of which 9 studies met the inclusion criteria. Interventions included proton pump inhibitors (n=3), H2 antagonists (n=5), surgery (n=1) and conservative management (n=1). Treatment time ranged from 1 week to 6 months. A temporal association between asthma and GOR was investigated in 4 trials and found to be present in a proportion of participants in these trials. Anti-reflux treatment did not consistently benefit lung function, asthma symptoms, nocturnal asthma or the use of asthma medications.

Conclusions: In asthmatic subjects with GOR, who were not specifically recruited on the basis of reflux-associated respiratory symptoms, there was no overall improvement in asthma following treatment for GOR. A subgroup of patients was reported to gain benefit but it appears difficult to predict responders. At present it is not possible to recommend medical

treatment of GOR as a means to control asthma. Future research should evaluate GOR therapy in a subgroup of asthmatics with reflux-induced asthma symptoms.

Citation: Gibson PG, Coughlan JL, Henry RL (Cochrane Review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update Software.

3 ***ALLERGEN IMMUNOTHERAPY FOR ASTHMA***

Abramson MJ, Puy RM, Weiner JM.
Date of most recent substantive amendment: 29/01/1998.

Abstract

Objectives: 1. To identify all published randomised controlled trials of allergen specific immunotherapy in asthma. 2. To estimate the overall efficacy of allergen specific immunotherapy upon asthmatic symptoms, medication requirements, lung function, nonspecific bronchial hyperreactivity (BHR) and allergen specific BHR.

Search strategy: A search of the Asthma database maintained by the Cochrane Airways Group at St George's Hospital Medical School, London identified 660 non-unique citations with the keywords Immunotherap* or Hyposensiti* or Desensiti*. This database included all studies published up to 1997 with the keywords Asthma or Wheez* from the Medline, Embase and Cinahl databases, together with other studies identified by handsearching.

Selection criteria: The review was restricted to randomised controlled trials (RCT). Only studies which focussed upon asthma were included. Allergen specific immunotherapy was defined as the subcutaneous administration of extracts of house dust mites, pollens, animal danders or moulds, chemically modified allergoids or antigen-antibody complexes. Although placebo controlled trials were methodologically stronger, studies which administered house dust or other relatively antigenically inactive preparations to the control group were also considered. Double blinded trials were preferred, but single blind and open studies were also reviewed for possible inclusion. At least one of the following clinical outcomes had to be reported: asthmatic symptoms, asthma medication requirements, lung function, nonspecific BHR or allergen specific BHR. Inclusion of studies in the review was decided by a simple majority of all three reviewers, who independently read the methods sections of papers identified by the search strategy and applied the stated criteria. Quality assessment was performed by 2 reviewers, who independently assessed the concealment of allocation.

Data collection and analysis: The comparisons were: allergen immunotherapy vs placebo, allergen immunotherapy vs antigenically inactive control, house dust vs placebo and allergen immunotherapy vs untreated control. These comparisons were performed separately for each outcome, whenever these results were reported.

Outcome data were extracted and entered into RevMan 3.0.1 for statistical analysis. Categorical outcomes were analysed as odds ratios (OR) and 95% confidence intervals (95%CI) calculated by Petoís method. Continuous outcomes were analysed as standardised mean differences (SMD). Fixed effects models were used to obtain summary statistics for the overall efficacy of allergen immunotherapy and x2 tests were performed to assess heterogeneity between studies.

Main results: Fifty-four randomised controlled trials published between 1954 and 1997 satisfied the inclusion criteria. There were 25 studies reporting immunotherapy for mite allergy, 13 studies of pollen allergy, eight studies of animal dander allergy, two studies of allergy to the mould Cladosporium and six studies that attempted simultaneous immunotherapy for multiple aeroallergens. Concealment of allocation was assessed as clearly

adequate in only 11 studies. The adequacy or otherwise of 40 studies could not be determined from the details published in the papers. Only three studies used a clearly inadequate method for concealment of allocation.

There was a significant overall improvement in asthma symptom scores following immunotherapy (combined SMD -0.52; 95% -0.70 to -0.35). Patients randomised to immunotherapy were also significantly less likely to report a deterioration in asthma symptoms than those randomised to placebo (OR 0.27; 95%CI 0.21 to 0.35). Asthma medication requirements were significantly reduced (SMD -0.51; 95%CI -0.74 to -0.28). Patients randomised to immunotherapy were also significantly less likely to require medication than those randomised to placebo (OR 0.28; 95%CI 0.19 to 0.42). There was no overall improvement in lung function following immunotherapy and marked heterogeneity between studies.

There was a modest reduction in nonspecific BHR following immunotherapy (SMD -0.32; 95%CI -0.55 to -0.1). Nonspecific BHR was also significantly more likely to improve among patients randomised to immunotherapy than those randomised to placebo (OR 0.13; 95%CI 0.05 to 0.34). There was a significant reduction in allergen specific BHR following immunotherapy (SMD -0.69; 95%CI-0.46 to -0.91). Patients randomised to immunotherapy were also significantly less likely to develop increased allergen specific BHR (OR 0.28; 95%CI 0.19 to 0.41).

Conclusions: Allergen specific immunotherapy significantly reduced asthma symptoms and medication requirements, but there was no consistent effect upon lung function. Allergen immunotherapy reduced allergen specific bronchial hyperreactivity to a greater extent than nonspecific bronchial hyperreactivity. Based on the data in this review, it is not possible to compare the size of improvement with immunotherapy to that obtained with other therapies for asthma. In particular, it is not possible to assess the effect of concurrent treatment with inhaled corticosteroids on the benefits to be derived from immunotherapy.

Immunotherapy may be considered when asthma is extrinsic and an unavoidable clinically relevant allergen can be identified. A specific effective extract should be used. When using this therapy, the question of side effects must be fully discussed with the patient and following an immunotherapy treatment the patient must be observed long enough to deal with any major systemic reactions and adequate resuscitation measures must be available because of the well-known possibility of anaphylaxis.

Citation: Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

4 *CAFFEINE FOR ASTHMA*

Bara AI, Barley EA.
Date of most recent substantive amendment : 22/02/1998.

Abstract

Objectives: To estimate the overall efficacy of caffeine upon lung function and to identify whether there is a need to control for caffeine consumption prior to lung function testing.

Search strategy: A search was carried out within the Cochrane Airways Group Register of Asthma and Wheeze randomised controlled trials (RCTs). The bibliography of each RCT was searched for additional trials. Authors of identified RCTs were contacted for other published and unpublished studies.

Selection criteria: Thirty-nine references were obtained from the literature search and independently assessed by the two reviewers. Full texts of potentially relevant trials were obtained. From these, six matched the inclusion criteria for this review.

Data collection and analysis: Data were extracted independently by the two reviewers. Since lung function outcomes were measured at different times and following different doses of caffeine, data for each outcome were grouped according to three time frames: 'short' - less than or equal to 2 hours; 'medium' - greater than 2 hours and less than or equal to 4 hours; 'long' - greater than 4 hours. Analyses were carried out using all caffeine doses and two subgroups based on the median dose: 'low' dose - 5mg or less of caffeine per kg of body weight; 'high' dose - greater than 5mg of caffeine per kg of body weight.

Main results: Caffeine, even at a low dose, compared to placebo was found to significantly improve lung function, measured in terms of FEV_1, FEF_{25-75} and specific airway conductance for up to 2 hrs post ingestion. This effect was sustained for FEF_{25-75} for over 4 hrs. Improvement was also seen in FEV_1 up to this time, however this effect did not reach statistical significance. No data were available for specific airway conductance after 2hrs.

Conclusions: It is recommended that patients be advised to withhold caffeine for at least four hours prior to lung function testing. Subjective patient benefits and clinical implications have not yet been thoroughly investigated. Caffeine improves airway function by a modest amount in asthmatic patients for up to four hours.

Citation: Bara AI, Barley EA. Caffeine for asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

5 *NEDOCROMIL SODIUM FOR PREVENTING EXERCISE-INDUCED BRONCHOCONSTRICTION*

Spooner CH, Saunders LD, Rowe BH.
Date of most recent substantive amendment 27/05/1998.

Abstract

Objectives: To assess the effectiveness and safety of using a single dose of nedocromil sodium (NCS) to prevent exercise-induced bronchoconstriction (EIB).

Search strategy: Computerised searches of the Cochrane Airways Review Group Asthma and Wheez* RCT register, Current Contents, and the Cochrane Controlled Trials Register were conducted and augmented with bibliographic searches of relevant studies, review articles, and textbooks. Personal communication with the drug manufacturer and authors of the included studies sought to identify additional published, unpublished, or in-progress trials that met the inclusion criteria. No language restrictions were applied.

Selection criteria: Randomised, double-blind, controlled trials that compared a single dose of NCS to a placebo in prophylactic treatment of EIB were eligible. Studies were included if: the participants had confirmed EIB, were subjected to an exercise challenge sufficient to trigger EIB, and the measures of lung function were reported as changes in forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR).

Data collection and analysis: The main outcomes assessed were changes in FEV_1 and PEFR caused by exercise, and any adverse effects caused by NCS. Changes in lung function were reported as the mean maximum percent (%) fall, or the mean % fall at different times post-exercise compared to pre-challenge baseline values. Methodological quality assessments and data abstraction were conducted independently by two reviewers using standard forms and validated assessment criteria. In the event of missing data, a pooled estimate obtained from the other included studies was used. Some results were estimated from graphs. Confirmation of study methodology and data abstraction was obtained from primary authors where possible. Results from similar studies were pooled and reported as the weighted mean difference (WMD) using the random effects model.

Main results: From fifty-one potentially relevant trials, twenty met the inclusion criteria, providing data on 280 participants. NCS was studied in 1 to 8 mg doses using a metered dose inhaler with or without a spacer, 15 to 60 minutes prior to a standardised exercise challenge test. NCS had a significant effect on inhibiting the severity of EIB in both adults and children. The WMD for the maximum % fall in FEV_1 was 15.6% (95% CI: 13.2, 18.1), and a protection effect of 51% (95% CI: 46, 55) over placebo. The WMD for the maximum % fall in PEFR was: 15.0% (95% CI: 8.3, 21.6) with a similar level of protection. There was additional evidence to indicate that the mean time to recover normal lung function was shortened: less than 10 minutes post-challenge using NCS compared with > 30 minutes after placebo. Significant differences in the inhibitory effect of NCS were demonstrated in subgroup analyses based on severity of EIB (% fall index less than 30% vs 30% or greater). The WMD for maximum % fall FEV_1 was 12.8% (95% CI: 10.0, 15.7) in mild EIB and 21.4% (95% CI: 17.2, 25.5) in severe EIB. A similar finding was demonstrated for the PEFR. There were no significant adverse symptoms or effects reported with the short term use of NCS.

Conclusions: The prophylactic use of NCS was effective in inhibiting significantly the severity and duration of EIB. This benefit appeared to be greater in patients with more severe EIB. Further research on comparing alternative drugs to NCS in EIB is required.

Citation: Spooner CH, Saunders LD, Rowe BH. Nedocromil sodium for preventing exercise-induced bronchoconstriction (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

6 *INFLUENZA VACCINATION IN ASTHMA: EFFICACY AND SIDE-EFFECTS*

Cates CJ, Jefferson TO, Bara AI.
Date of most recent substantive amendment: 15/07/1998.

Abstract

Objectives: To assess the efficacy and side-effects of influenza vaccination in preventing morbidity and mortality in asthmatic patients.

Search strategy: Randomised controlled trials were identified from the Cochrane Airways Group Asthma Register which is a compilation of systematic searches of CINAHL, EMBASE and MEDLINE and hand searching of 20 respiratory journals.

Selection criteria: All randomised controlled trials involving asthmatic children (over 2 years of age) or adults given any type of influenza vaccination were included. Outcome measures included exacerbation rate, admission to hospital, pneumonia, asthma symptom scores, lung function measurements and mortality. These were separately analysed for the week following immunisation (adverse effects) and the following six months (protective effects). Two reviewers independently selected potentially relevant abstracts identified from the register, and assessed the full papers for inclusion and methodological quality. Tests for agreement between reviewers were performed.

Data collection and analysis: Data extraction was performed by two reviewers and checked with the authors where possible. Missing data was obtained from the authors where possible. Data were analysed using Review Manager version 3.1. Sensitivity analyses and sub-group analyses were not possible due to the lack of suitable data.

Main results: Nine studies were included in this review, of which four were of high methodological quality. There are currently no data from randomised controlled trials to confirm the protective effect of influenza vaccination against asthma exacerbation due to influenza infection. Furthermore, one well designed study [Nicholson, 1998] has shown a small additional risk of asthma exacerbation following administration of inactivated influenza vaccine in adults (Risk Difference 3.1%, 95% Confidence Interval 0.3% to 5.8%).

Conclusions: Large randomised placebo-controlled trials are required to further assess the benefits and risks of different influenza vaccinations for asthmatic patients in the community.

Citation: Cates CJ, Jefferson TO, Bara AI. Influenza vaccination in asthma: efficacy and side-effects (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

Critically Appraised Recommendations

1 SO_2, exercise exposure and lung function in asthma

Recommendation: *"Studies have failed to show that air pollutants are an important cause of asthma in Australia, but pollutants may be linked to asthma exacerbations and, in some regions, to increased aeroallergen sensitisation."*

Question: *Does brief exposure to SO_2 under laboratory conditions with episodes of exercise, have an adverse effect on lung function in asthmatic subjects?*

Answer: Airway obstruction (Specific Airway Resistance - SRaw) is increased in asthmatics by brief exposure to SO_2 when administered during exercise. Measures of airway obstruction in asthmatics were adversely affected by brief chamber exposures to SO_2 under exercise. The level at which an effect occurred varied from 0.25 to 1.0 ppm and a dose response relationship was evident.

Search Strategy: Medline 1966 to December 1997 was searched using the terms 'asthma' and 'air pollution' or 'SO_2' or 'sulphur dioxide' or 'sulfur dioxide' or 'SO2' limiting the search results to randomised controlled trials (RCTs).

Results: A review of 18 abstracts yielded: 7 RCTs and one CCT relevant to the effect of SO_2 on asthma.

Trial	Interventions	n	Age Mean	% male	Significant Outcomes
Linn (1987)	Atopic, asthmatic (mild & severe) and normal subjects randomly exposed for one hour to 0.0, 0.2, 0.4, 0.6 ppm SO_2, incorporating 3 x 10 minute exercise periods.	85	18-46	63	Exercise in SO_2 significantly affected SRaw and FEV_1 in asthmatic subjects. Although severe asthmatics experienced greater exercise induced bronchospasm, their response to SO_2 was similar to mild asthmatics at higher concentrations of SO_2.
Horstman (1986)	Subjects sensitive to inhaled methacholine were randomly exposed for 10 mins to 0, 0.25, 0.5, 1.0 ppm SO2 at 26° C 70% relative humidity while breathing naturally and exercising moderately.	27	25 (±4yrs)	100	Dose response curves to SO_2 were constructed for each subject. Increasing doses of SO_2 caused increasing airway obstruction however, substantial variability was observed. The SO_2 level that produced a 100% rise in SRaw varied from 0.21 to 1.9ppm and a median of 0.75ppm.
Bethel (1985)	Subjects randomly exposed to filtered air at ambient temperature and ? humidity with or without 0.25 ppm SO_2 in a chamber while heavily exercising.	19	29 (±6yrs)	84	Exposure to SO_2 caused a modest but significant enhancement of the increase in specific airway resistance (SRaw) associated with exercise.
Roger (1985)	Subjects hypersensitive to methacholine were randomly exposed to air or 0.00, 0.25, 0.5 and 1.0ppm SO_2 while breathing normally and exercising for 10 minute intervals.	28	19-34	100	Specific airway resistance was not affected by exercise in SO_2 0.25ppm compared with exercise in clean air. SRaw was increased two fold and three fold by exercise in 0.5 and 1.0 ppm SO_2 respectively above the increases reported in clean air.

Schachter (1984)	10 asthmatic and 10 healthy subjects randomly exposed in a chamber to 0.0, 0.25, 0.50, 0.75 and 1.00 ppm SO2 for 40 minutes. Subjects exercised for the first 10 minutes at 450 kpm/min. A second study was conducted at 1.0 and 2.0 ppm SO_2 without exercise.	10	26.1 (± 6 yrs)	40	Exercise in 1.00 ppm SO_2 significantly increased airway resistance and reduced FEV_1. A dose-response relationship was present. No effect of SO_2 was noted when asthmatic subjects did not exercise.
Bethel (1984)	7 mildly asthmatic subjects were exposed to humid room temperature air (with and without SO_2 0.5 ppm) and cold dry air (with and without SO_2 0.5 ppm) using a level of eucapnic hyperventilation that did not cause bronchoconstriction with either SO_2 or cold air alone.	7	24-36 yrs	N/S	SRaw increased significantly when SO_2 0.5 ppm was combined with cold dry air compared with all other exposures.
Bethel (1983)	10 mildly asthmatic subjects randomly exposed to filtered air with or without 0.5 ppm SO_2 in a chamber whilst exercising at 750kpm/min for 5 minutes	10	28 (±5 yrs)	80	SRaw increased significantly more with exercise in 0.5 ppm SO_2 than with exercise in SO_2-free air. There was a high degree of variation in response to SO_2 between subjects.
Sheppard (1981)	7 mildly asthmatic subjects randomly assigned to breath 0.5 and 0.25 ppm SO_2 or filtered humidified air in a chamber while exercising at 400 kpm/min on a cycle ergometer for 10 mins. A second study was conducted at the same levels without exercise.	7	20-30yrs	86	SRaw was significantly increased after exercise in both 0.25 and 0.5 ppm SO_2 compared with exercise in SO_2-free air. A dose-response relationship was evident.

Comments/Limitations:

Factors such as a decrease in air temperature, a change in relative humidity or an increase in minute ventilation as may occur with different exercise loads may influence the bronchoconstrictive effects of SO_2 and may contribute to the high degree of variability in airway response of asthmatic subjects to SO_2. Further, specific airway resistance may not be the most appropriate surrogate measure of bronchoconstriction.

References:

1 Avol E, Linn W, Whynot J, Anderson R, Shamoo D, Valencia L, Little D, Hackney J. Respiratory dose-response study of normal and asthmatic volunteers exposed to sulfuric acid aerosol in the sub-micrometer size range. Toxicology & Industrial Health 1988;4(2):173-84.

2 Bethel R, Epstein J, Sheppard D, Nadel J, Boushey H. Sulfur dioxide-induced bronchoconstriction in freely breathing, exercising, asthmatic subjects. American Review of Respiratory Disease 1983;128:987-990.

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5 Horstman D, Roger L, Kehrl H, Hazucha M. Airway sensitivity of asthmatics to sulfur dioxide. Toxicology and Industrial Health 1986;2:289-98.
6 Linn W, Avol E, Peng R, Shamoo D, Hackney J. Replicated dose-response study of sulfur dioxide effects in normal, atopic, and asthmatic volunteers. American Review of Respiratory Disease 1987;136(5):1127-34.
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Prepared by:

1. Jennifer Coughlan 28th August, 1998
2. Anita Chalmers 4th November, 1998

Reviewed by Content Expert: Professor Michael Hensley 4th November, 1998

2 NO_2 exposure in combination with exercise

Recommendation: *"Studies have failed to show that air pollutants are an important cause of asthma in Australia, but pollutants may be linked to asthma exacerbations and, in some regions, to increased aeroallergen sensitisation. A sensible approach on high pollution days is to avoid exercise, stay indoors where possible, and have ready access to bronchodilators."*

Question: *Does brief exposure to NO_2 combined with exercise under laboratory conditions, alter lung function in subjects with asthma?*

Answer: Short exposures to NO_2 at levels between 0.3 to 3.0 ppm under laboratory conditions produced no clinically significant effect on lung function

Search Strategy: Medline 1966 to December 1997 was searched using the terms 'asthma' and 'nitrogen dioxide' or NOx, limiting the search results to randomised controlled trials (RCTs).

Results: A review of 19 abstracts yielded five randomised controlled trials which investigated the effects of short exposures to NO_2 or nitrous acid which incorporated periods of exercise.

Trial	Interventions	n	Age Mean	% Male	Significant Outcomes
Avol (1988)	Moderate to severe adult asthmatic volunteers were randomly exposed to 0.0, 0.3 and 0.6 ppm NO_2 with periods of exercise. A subset were also exposed to Los Angeles ambient air with NO_2 concentrations of 0.086 +/- 0.024 ppm (mean & s.d.).	59	30 (±8yrs sd)	46%	Nil. Ambient air produced the largest (but still non-significant) mean change in lung function.
Linn (1986)	Mild asthmatic subjects exposed via a chamber to 0.0, 0.3, 1.0 and 3.0 ppm NO_2 for 1 hr with moderate to heavy 10 minute bouts of exercise in 22° C and relative humidity near 50%.	21	24 (±5yrs sd)	71%	Exercise induced significant bronchoconstriction regardless of NO_2 level. No significant untoward response to NO_2 was observed at any exposure concentration.
Rubenstein (1990)	Clinically stable asthmatic subjects exposed to 0.3ppm or filtered air in an environmental room for 30 mins. Exercise was undertaken for the first 20 mins of the 30 min exposure.	9	29 (±4yrs sd)	55%	NO_2 did not significantly alter lung function measured by FEV_1/FVC and specific airway resistance. NO_2 did not potentiate airway responsiveness to SO_2.
Vagaggini (1996)	7 normal, 8 mild asthmatic and 7 COPD subjects randomly exposed to air or 0.3ppm nitrogen dioxide under exercise.	8	29 (±14yrs sd)	50%	Short term exposure to NO_2 did not significantly alter lung function as measured by FEV_1 in exercising asthmatic subjects.

Comments/Limitations:.

These studies measured the impact of short term exposure to various concentrations of NO_2 administered by under laboratory conditions by a variety of means and, as such, cannot be used as a surrogate of the effect of long-term, indoor and outdoor exposure to ambient air-pollution on the lung function of asthmatic subjects. The generalisability to ambient air is further limited by these studies using a single air pollutant.

References:

1 Avol E, Linn W, Peng R, Valencia G, Little D, Hackney J. Laboratory study of asthmatic volunteers exposed to nitrogen dioxide and to ambient air pollution. American Industrial Hygiene Association Journal 1988;49(4):143-9.Step 3 Q. 18, 18.1c.

2 Beckett W, Russi M, Haber A, Rivkin R, Sullivan J, Tameroglu Z, Mohsenin V, Leaderer B. Effect of nitrous acid on lung function in asthmatics: a chamber study. Environmental Health Perspectives 1995;103(4):372-5.Step 3 Q. 18.1c.

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5 Vagaggini B, Paggiaro P, Giannini D, Franco A, Cianchetti S, Carnevali S, Taccola M, Bacci E, Bancalari L, Dente F, Giuntini C. Effect of short-term NO2 exposure on induced sputum in normal, asthmatic and COPD subjects. European Respiratory Journal 1996;9:1852-7.Step 3 Q. 18.1c.

Prepared by:

1. Jennifer Coughlan 30th July, 1998
2. Anita Chalmers 4th November, 1998

Reviewed by Content Expert: Professor Michael Hensley 4th November, 1998

3 NO_2 in combination with SO_2

Recommendation: *"Studies have failed to show that air pollutants are an important cause of asthma in Australia, but pollutants may be linked to asthma exacerbations and, in some regions, to increased aeroallergen sensitisation. A sensible approach on high pollution days is to avoid exercise, stay indoors where possible, and have ready access to bronchodilators."*

Question: *Does brief exposure to NO_2 in combination with SO_2 under laboratory conditions increase airway hyperresponsiveness in asthmatic subjects?*

Answer: Exposure to NO_2 in combination with SO_2 increased airway hyperresponsiveness to house dust mite in atopic asthmatic subjects.

Search Strategy: Medline 1966 to August 1998 was searched using the terms 'asthma' and 'nitrogen dioxide' or NOx, limiting the search results to randomised controlled trials (RCTs).

Results: A review of 19 abstracts yielded 2 randomised controlled trials which investigated the effects of brief exposures of atopic asthmatic patients to NO_2 in combination with SO_2 under laboratory conditions.

Trial	Subjects	N	Age mean (range)	Male %	Significant Outcomes
Ruznak (1996)	Mild atopic asthmatics were randomly exposed for 6 hours to air or 0.4 ppm NO_2 plus 0.2 ppm SO_2. All subjects were then challenged with HDM allergen 10 mins, 24 hrs and 48 hrs post exposure.	13	28.1 (21-39)	77%	Exposure to SO_2 and NO_2 for 6 hours significantly increased airway hyperresponsiveness to HDM. The maximal effect was observed at 24 hours post exposure.
Devalia (1994)	Mild atopic asthmatics randomly exposed to either air, SO_2, NO_2 or SO_2 and NO_2 over 6 hours. All subjects were then challenged with HDM allergen.	8	27.6 (18-45)	50%	Neither SO_2, NO_2 nor the combination caused a reducation in pre-challenge FVC or FEV_1. SO_2, and NO_2 increased airway hyperresponsiveness to HDM but not significantly. The combination of SO_2 and NO_2 cuased a significant increase in airway hyperresponsiveness.

Comments / Limitations:

Exposure concentrations in these studies were consistent with high pollution days. As these studies are exposure to laboratory air pollution rather than avoidance of ambient indoor or outdoor air pollution they provide support for the rationale that air pollution increases sensitivity to aeroallergens but do not support the recommendation to stay indoors.

References:

1 Devalia J, Rusznak C, Herdman M, Trigg C, Tarraf H, Davies R. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. Lancet 1994;344(8938):1668-71. Step 3 Q. 18, 18e.

2 Rusznak C, Devalia J, Davies R. Airway response of asthmatic subjects to inhaled allergen after exposure to pollutants. Thorax 1996;51:1105-8. Step 3 Q. 18, 18e.

Prepared by:

1. Jennifer Coughlan 31st July, 1998
2. Anita Chalmers 4th November, 1998

Reviewed by Content Expert: Professor Michael Hensley 4th November, 1998

4 NO_2 at rest

Recommendation: *"Studies have failed to show that air pollutants are an important cause of asthma in Australia, but pollutants may be linked to asthma exacerbations and, in some regions, to increased aeroallergen sensitisation. A sensible approach on high pollution days is to avoid exercise, stay indoors where possible, and have ready access to bronchodilators."*

Question: *Does brief exposure to NO_2 at rest under laboratory conditions increase allergen or methacholine-induced airway hyperresponsiveness in atopic asthmatic subjects?*

Answer: Exposure to NO_2 appears to have a small potentiating effect on airway hyperresponsiveness to allergen in atopic asthmatic subjects. Airway responsiveness to chemical challenge appears to be enhanced by exposure to NO_2 under laboratory conditions but varies with the level of exposure with a threshold somewhere between 0.3 and 0.5 ppm.

Search Strategy: Medline 1966 to August 1998 was searched using the terms 'asthma' and 'nitrogen dioxide' or NO*, limiting the search results to randomised controlled trials (RCTs).

Results: A review of 19 abstracts yielded 6 randomised controlled trials which investigated the effects of brief exposures of atopic asthmatic patients to NO_2 under laboratory conditions which used a methacholine, histamine or allergen challenge to measure airway hyperreactivity.

Short term laboratory NO_2 exposure at rest - allergen challenge

Trial	Interventions	n	Age Range	Male %	Significant Outcomes
Strand (1997)	Mild asthmatic subjects with allergy to pollen were randomly exposed to 0.26 ppm NO_2 for 30 mins, given an allergen challenge to timothy or birch pollen at 4 hours and a histamine challenge at 24 hours.	18	30 yrs (18-50)	50%	Late asthmatic response was enhanced by NO_2. PEF after **pollen challenge** was on average 6.6% lower (p=0.02) after exposure to NO_2 than after exposure to air.
Tunnicliffe (1994)	Mild asthmatic subjects with a positive skin prick test to HDM allergen were exposed in random order to 1 hr of air or 100 or 400 ppb NO_2 followed immediately by HDM & histamine challenge at 7 and 24 hours later.	10	16-60	40%	Both early and late asthmatic response was enhanced by 400ppb NO_2. FEV_1 after HDM challenge was on average 4-5% lower after exposure to 400 ppb NO_2 than after exposure to air.

Short laboratory NO_2 exposure at rest - methacholine, histamine or carbachol challenge

Trial	Interventions	n	Age Range	Male %	Significant Outcomes
Salome (1996)	Subjects with atopic asthma who required daily medication. Double blind random 1 hour exposures to ambient air or 0.3 or 0.6 ppm NO_2 in ambient air or ambient air + combustion by-products + NO_2 to give a total of 0.6 ppm.	20	9 adults (19-65yr) and 11 children (7-15yr)	2 (22%) 6 (55%)	Exposure to NO_2 in ambient air or mixed with combustion by-products had no significant effect on symptoms or lung function. There was a small but significant increase in AHR to histamine challenge after exposure to 0.6ppm NO_2 in ambient air but not when combined with combustion by-products.
Mohsenin (1987)	Asthmatic subjects were randomly exposed to 0.5 ppm NO_2 or air.	10	30 yrs (22-40)	30%	Asthmatics exposed to 0.5 ppm NO_2 developed heightened airway reactivity to methacholine as measured by the dose required to bring about a greater than 40% reduction in V_p40.
Hazucha (1983)	15 normal and 15 atopic asthmatic subjects were randomly exposed in a double-blind cross over study to air or 0.1 ppm NO_2 for one hour at rest.	15	28yrs (21-46)	100%	NO_2 had no effect on specific airway resistance, forced random noise impedance spectrum nor response to bronchial inhalation challenge using methacholine.
Orehek (1976)	20 mild asthmatic subjects of whom 16 were atopic were randomly exposed to 0.1 ppm NO_2 or air for one hour while panting at 0.5 liters/s.	20	26yrs (15-64)	65%	13 of the 20 subjects were classified as 'NO_2 responders' & showed a small but significant increase in SRaw after NO_2 exposure. The dose of carbachol required to bring about a twofold increase in SRaw was significantly reduced after NO_2 exposure.

Comments/Limitations:

These studies used laboratory conditions to measure the influence of NO_2 on airway hyperresponsiveness to pollens or HDM or to chemical agents which impact directly on airway tissue to cause bronchoconstriction (methacholine, histamine, carbochol). Combination of the above studies to answer the question is limited because of inter-study variations in the following:

1) Interventions (i.e. differing levels of NO_2 concentration; duration of exposure; differences in humidity and temperature; requirement to pant or not);

2) Timing and manner of measuring airway responsiveness (i.e. various allergen challenges; methacholine challenge; carbachol challenge) and,

3) Different endpoints (Vp40, PD40, SRaw, FEV_1, PEF).

4) Subject selection (i.e. atopy, smoking etc.)

Further, it is not possible to use the results as a surrogate measure of asthma exacerbations resulting exposure to NO_2 in the presence of other pollutants found in ambient air. It is necessary to have additional information about: the relative indoor and outdoor levels of NO_2; the presence of other pollutants in ambient air and the level of activity, hence ventilation.

In summary, the data support the hypothesis that higher levels of NO_2 increase bronchial hyperresponsiveness but the available data do not support or refute the recommendation to stay indoors.

References:

1 Hazucha M, Ginsberg J, McDonnell W, Haak E, Pimmel R, Salaam S, House D, Bromberg P. Effects of 0.1ppm nitrogen dioxide on airways of normal and asthmatic subjects. Journal of Applied Physiology: Respiratory, Environmental & Exercise Physiology 1983;54:730-9.

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5 Strand V, Rak S, Svartengren M, Bylin G. Nitrogen dioxide exposure enhances asthmatic reaction to inhaled allergen in subjects with asthma. American Journal of Respiratory and Critical Care Medicine 1997;155:881-7.

6 Tunnicliffe W, Burge P, Ayres J. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. Lancet 1994;344(8939-8940):1733-6.

Prepared by:

1. Jennifer Coughlan 30th July, 1998
2. Anita Chalmers 13th August, 1998

Reviewed by Content Expert: Professor Michael Hensley 4th November, 1998.

5 Antibiotic use during exacerbations of asthma

Recommendation: *"Treat bacterial infection if present. Asthma can cause discoloured sputum which does not necessarily indicate infection."*

Question: *Does treatment with antibiotics during an exacerbation of asthma reduce the time course of the exacerbation?*

Answer: Level II evidence does not support the routine use of antibiotics for the treatment of an asthma exacerbation in either children or adults who do not demonstrate clinical evidence of a bacterial infection.

Search Strategy: Medline 1966 to December 1997 was searched using the terms 'asthma' and 'antibiotics'.

Results: Thirty-five RCTs were retrieved. Five RCTs were included after review of the abstracts and three RCTs were included after review of the full text version of the articles. One paper (Snyder, 1970) was excluded as it reviewed the use of prophylactic antibiotics rather then the use of antibiotics during an exacerbation and another paper was excluded because it reviewed the use of a steroid sparing agent rather than an antibiotic (Ball, 1990). This review is based on the remaining three studies which investigated the use of antibiotics in the treatment of an asthma exacerbation. Asthma status was moderate to severe in these studies. Two studies investigated adults, the third, children.

Trial	Interventions	n	Age Mean	% Male	Outcomes
Sachs (1995)	Amoxycillin 500mg tds or trimoxazole 960mg bd vs placebo given to patients in general practice with COPD and asthma. All patients treated with corticosteroids.	71	51.7	42%	No significant difference between the three treatment arms for symptoms, time to recover, PEF, sputum purulence or relapses.
Graham (1982)	Amoxycillin 500mg tds vs placebo given to patients hospitalised for an asthma exacerbation All patients treated with corticosteroids.	60	39.3	42%	No significant difference between the treatment and placebo groups for FEV_1, PEF, length of stay. No difference between groups in sputum cultures for Haemophilus influenzae or Streptococcus pneumoniae on admission or discharge.
Shapiro (1974)	Hetacillin 100mg/kg/24hr IV vs identically packaged placebo given to children hospitalised for asthma. All patients treated with corticosteroids.	44	8.6	Not stated	No significant difference between the treatment and placebo groups for length of stay. None of the patients had clinical evidence of bacterial disease.

Comments/Limitations: Only 3 studies addressed the question; 2 studied adults and 1 children. The subjects that Sachs studied were patients with predominantly non-reversible airways disease.

References:

1 Ball B, Hill M, Brenner M, Sanks R, Szefler S. Effect of low-dose troleandomycin on glucocorticoid pharmacokitentics and airway hyperresponsiveness in severely asthmatic children. Annals of Allergy 1990;65(1):37-45. Step 3 Q. 8.

2 Graham V, Milton A, Knowles G, Davies R. Routine antibiotics in hospital management of acute asthma. Lancet 1982;1(8269):418-20.Step 3 Q. 8.

3 Sachs A, Koeter G, Groenier K, van der Waaij D, Schiphuis J, Meyboom-de Jong B. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. Thorax 1995;50(7):758-63. Step 3 Q. 8.

4 Shapiro G, Eggleston P, Pierson W, Ray C, Bierman C. Double-blind study of the effectiveness of a broad spectrum antibiotic in status asthmaticus. Pediatrics 1974;53(6):867-72. Step 3 Q. 8.

5 Snyder R, Stiefel F. Prophylactic antibiotics in asthmatic children. Annals of Allergy 1970;28(7):307-12. Step 3 Q. 8.

Prepared by:

1. Jennifer Coughlan 30 November, 1997

6 Allergen avoidance and asthma

Recommendation: *"Continued exposure to allergens and other trigger factors can lead to worsening of asthma. Avoidance of trigger factors may improve asthma"*

Question: *Does avoidance of ingested allergen prevent the development of asthma?*

Answer: An avoidance of known allergen producing foods (ie peanuts, cow's milk and egg) by the mother during pregnancy has no long term potential to prevent the onset of asthma. However, avoidance of cow's milk formula or soy formulae in the 1st 6 months of life may reduce the risk of the development of asthma in high risk infants with a family history of atopy.

Search Strategy: Medline 1966 to December 1997 was searched using the terms 'asthma' and 'allerg$' limited to English, human and randomised controlled trials (RCTs).

Results: Three hundred and forty three citations of randomised controlled trials (RCTs) were retrieved. A title search yielded 16 possible primary prevention RCTs. Eight papers reporting 5 RCTs were included after review of the abstracts.

Maternal Avoidance

Trial	Interventions	N	Age Range	% Male	Significant Outcomes
Zeiger (1995) Zeiger (1993) Zeiger (1992)	Maternal avoidance of cow's milk, egg, and peanut during 3rd trimester & lactation. Infant use of casein hydrolysate; avoidance of cow's milk, corn, soy, citrus and wheat for 12 months; egg peanut and wheat for 24 months.	at 2 yrs n= 288 at 4 yrs n= 125 at 7 yrs n=165	0-2 4 yrs 7 yrs	N/S	Reduced cumulative prevalence of atopy (eczema, uticaria, GI disease, and positive SPT to foods) at 12 months. At age 7 years (after a loss of almost 50% of subjects) there was no difference between the groups for: food allergy, atopic dermatitis, allergic rhinitis, asthma, any atopic disease, lung function, food or aeroallergen sensitization, serum IgE level, presence of nasal eosinophils or nasal basophilic cells.
Hide (1994) and Arshard (1992)	Mothers avoided allergenic foods (milk, egg, fish and nuts), and avoided feeding infants these foods, and soya, wheat and orange up to the age of 12 months. Acaricides every 3 months	120	0-1yrs Follow-up to 2 years	51%	After 1 year, infants in the prophylactic group were less likely to have developed an allergy, asthma or eczema. At age 2 years, while there was less atopy in the prophylactic group the reduced risk of asthma prevalence remained lower but not statistically significant.
Falth-Magnusson (1992)	Maternal avoidance of cow's milk and egg from 3rd trimester until delivery. No intervention for infants.	209 mothers 155 infants at 5 years	0-5 yrs	N/A	Persistent food intolerance to egg was significantly more common in treatment group. No difference in asthma or allergic rhinitis at 5 years.

Infant Avoidance

Trial	Interventions	N	Age Range	% Male	Significant Outcomes
Chandra RK (1997)	Non-breast fed, high risk infants with a family history of atopy randomised to receive partial whey hydrolysate, or cows' milk, or soy formula until 6 months. A further 72 high risk infants who were breast fed > 4 mths were also followed.	216 72	0-5yrs	N/A	After 5 years fewer subjects in the breast-fed and the whey hydrolysate formula groups had developed eczema or asthma. The whey hydrolysate group also recorded fewer food allergies than the other formula groups as determined by double-blind placebo controlled food challenges.
Lucas (1990)	Preterm infants given donor breast milk, or high protein preterm formula (Trial A); term compared with preterm formula (Trial B).	777 Trial A 331 Trial B	pre-term to 18mth	N/A	At 18 months after term there was no difference in the incidence of allergic reactions. In infants with family history of atopy, preterm formula (i.e. high cow's milk protein) had increased risk of atopic disease (esp. eczema).

Comments/Limitations: The reported associated risk factors for atopy included male sex, maternal nonwhite ethnicity and asthma, household smoking, maternal allergy, family history of atopy and pre-term formula without breast-milk supplementation.

The primary limitation in comparisons was that some studied maternal avoidance combined with infant avoidance, some studied maternal avoidance alone while others studied infant food allergen avoidance. This limits the potential to combine the results. Further, the lack of a clear definition of asthma in the first 5 years of life presents the opportunity for inconsistent reporting of the key outcome.

References:

1 Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance of development of allergic disorders in infancy. The Lancet 1992;339(8808):1493-7.

2 Chandra RK. Five-year follow-up of high -risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. Journal of Pediatric Gastroenterology and Nutrition 1997; 24(4):380-8.

3 Hide D, Matthews S, Matthews L, al e. Effect of allergen avoidance in infancy on allergic manifestations at age two years. Journal of Allergy & Clinical Immunology 1994;93(5):842-6.

4 Falth-Magnusson K, Kjellerman N. Allergy prevention by maternal elimination diet during late pregnancy - A 5 year follow up of a randomized study. Journal of Allergy and Clinical Immunology 1992;89:709-13.

5 Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomised prospective study. BMJ 1990; 300(6728):837-40.

6 Zeiger R, Heller S. Development of nasal basophilic cells and nasal eosinophils from age 4 months through 4 years in children of atopic parents. Journal of Allergy and Clinical Immunology 1993; 91(3):723-34.

7 Zeiger R, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. Journal of Allergy and Clinical Immunology 1995;95(6):1179-90.

8 Zeiger R, Heller S. Mellon M, et al. Effect of combined maternal and infant food allergen avoidance on development of atopy in early infancy: a randomised study. Journal of Allergy and Clinical Immunology 1989;84:72-89.

Prepared by:

1. Jennifer Coughlan 14th February, 1998
2. Frank Thien 27th July, 1998.

7 Avoidance of cat dander

Recommendation: *"If specific triggers are demonstrated, advise on reducing exposure to them."*

Question: *Does avoidance of cat dander improve asthma control?*

Answer: There are currently no randomised controlled trials on the effects of cat allergen reduction on asthma severity to support a recommendation for this therapy in asthma.

Search Strategy: The Cochrane Controlled Trials Register was searched using the terms 'cat' OR 'fel' AND 'allerg*'

Results: A review of 43 abstracts yielded 2 potentially randomised controlled trials. After examination of the full text versions of these papers, one was excluded as it did not distinguish whether the effects observed were secondary to house dust mite or cat allergen avoidance.

Trial	Interventions	n	Age Mean Range	Male %	Significant Outcomes
Wood (1998)	Cat-allergic subjects who were living with at least one cat were randomly allocated to have a HEPA air filter or placebo filter placed in their bedrooms for a 3 month period. Cats were excluded from the bedrooms for the period of the study.	35	36.4 (23-6)	69	Airborne levels of Fel D 1 were reduced in the active filter group ($p = 0.045$), but there was no reduction in the amount of Fel D 1 in settled dust. There was no change in nasal or chest symptom scores, medication use or peak-flow rates in the active filter group.

Comments/Limitations: This study tried to determine whether rhinitis and asthma symptoms could be improved in cat-allergic subjects by reducing airborne cat allergen with HEPA air filters. Although cats were excluded from the bedroom, they were not excluded from the house. The reduction in airborne Fel D 1 levels in the treatment group was 43%. There was no reduction in Fel D 1 concentration in settled dust. Consequently the study provides only a limited answer to the question posed because the low efficacy of the cat allergen avoidance strategy in reducing exposure to Fel D 1. In summary, there are currently no randomised controlled studies available on the effects of cat allergen reduction on asthma severity to support a recommendation for cat avoidance.

References:

1. Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. Am J Respir Crit Care Med 1998;158:115-20.

Reviewed by Content Expert:

1. Dr Richard Douglass 27 April, 1999.

Critically Appraised Recommendations in Progress

1 Does exposure to cold air increase asthma severity/ exacerbations?

Cochrane Systematic Reviews in Progress

1 Allergen responsiveness of asthmatics and its association with exposure to nitrogen dioxide
2 Dietary avoidance of cow's milk protein for preventing asthma in children
3 Dietary marine fatty acids for asthma
4 Tartrazine exclusion for allergic asthma
5 Does high salt intake increase the severity of asthma?
6 What is the efficacy of vitamin C supplementation in the treatment of asthma
7 Does exposure to environmental tobacco smoke increase asthma severity/exacerbations
8 What is the effect of influenza vaccination on asthma?

Research Questions

1 Does low anti-oxidant intake increase the severity of asthma?
2 Does exposure to SO2 increase asthma severity/ exacerbations?
3 Does exposure to PM10 increase asthma severity/ exacerbations?
4 Does exposure to NOx increase asthma severity/ exacerbations?
5 Does avoidance of SO2 improve asthma/reduce severity/reduce exacerbations?
6 Does avoidance of PM10 improve asthma/reduce severity/reduce exacerbations?
7 Does avoidance of NOx improve asthma/reduce severity/reduce exacerbations?
8 Does avoidance of cold air improve asthma/reduce severity/reduce exacerbations?
9 Does reduction of environmental tobacco smoke improve asthma control?
10 Does avoidance of non-sensitising occupational irritants improve asthma control?
11 Occupational Irritants: Does avoidance of non-sensitising occupational irritants reduce asthma severity?
12 Does avoidance of non-sensitising irritants reduce exacerbations?
13 Do patients instigate allergen avoidance procedures following the identification of specific sensitisation by means of skin tests, IgE or RAST measurements?
14 Does avoidance of domestic sensitisers improve asthma?
15 Does avoidance of domestic sensitisers reduce asthma severity?
16 Does avoidance of domestic sensitisers reduce asthma exacerbations?
17 Does avoidance of occupational sensitisers improve asthma?
18 Does avoidance of occupational sensitisers reduce asthma severity?
19 Does avoidance of occupational sensitisers reduce asthma exacerbations?
20 Does sleeping in a warm room prevent nocturnal exacerbations of asthma?
21 Do patients instigate allergen avoidance procedures if advised to do so by their doctor?
22 Does allergen avoidance reduce the severity of asthma?
23 Does influenza increase the severity of asthma?

STEP 4: MAINTAIN BEST LUNG FUNCTION – OPTIMISE MEDICATION PROGRAM

Cochrane Systematic Reviews

1 Holding chambers versus nebulisers for beta-agonist treatment of acute asthma
2 Anti-cholinergic drugs for wheeze in children under the age of two years
3 Methotrexate as a steroid sparing agent in adult asthma
4 Long acting beta-agonists versus theophylline for maintenance treatment of asthma

Critically Appraised Recommendations

1 Does addition of long-acting beta-agonists to inhaled steroids in adult patients with mild-to-moderate asthma lead to better outcomes than management with inhaled steroids alone?
2 Theophylline versus long-acting beta-agonists

Critically Appraised Recommendations in Progress

There are 14 critically appraised recommendations in progress.

Cochrane Systematic Reviews in Progress

There are 20 Cochrane Systematic Reviews in progress.

Research Questions

Fourteen research questions have been identified for this step.

Cochrane Systematic Reviews

1 *HOLDING CHAMBERS VERSUS NEBULISERS FOR BETA-AGONIST TREATMENT OF ACUTE ASTHMA*

Cates C J.
Date of most recent substantive amendment: 13/02/1998.

Abstract

Objectives: The objective of this review was to compare holding chambers to wet nebulisation for the delivery of beta-agonists in the treatment of acute asthmatic exacerbations.

Search strategy: Randomised controlled trials were identified using the Cochrane Airways Review Group and the Cochrane Controlled Clinical Trials Registers.

Selection criteria: All randomised controlled trials (RCTs) involving adults and/or children (from 2 years of age), where beta-agonists delivery was compared using wet nebulisation and holding chambers. Outcome measures included: admission to hospital, duration in the emergency department (ED), change in respiratory rate, blood gases, pulse rate, tremor, symptom score and lung function. One reviewer selected potentially relevant articles. Methodological quality was independently assessed by a second reviewer. Kappa tests were performed for agreement between reviewers.

Data collection and analysis: Data extraction was performed by a single reviewer (CJC). Missing data, (e.g. standard deviation for changes in lung function) were obtained from authors or estimated. Sensitivity analyses were performed to determine the impact of including estimated results from other data in the papers. The data were analysed using Cochrane Review Manager 3.0. The results for adults and children have been analysed separately due to significant heterogeneity in the pooled results. Only the results from multiple treatment studies have been pooled to avoid confounding by differences in drug delivery to the airways in single treatment studies.

Main results: 112 abstracts were originally identified from the database; of these 44 were identified from their title, keywords, MESH headings and abstracts as potentially relevant and were selected for detailed examination of the full paper. This review is restricted to 12 articles, which met the inclusion criteria. One further article has been published since the previous version of this review. Inclusion of this trial has not altered the conclusions of this review. No significant difference was found in hospital admission rate in either adults or children when the two delivery methods were compared. [Adults: odds ratio (OR) = 1.12; 95% confidence interval (CI): 0.45 to 2.76. Children OR = 0.71; 95% CI: 0.23 to 2.23.] Significant differences were demonstrated in other outcomes, with holding chambers resulting in less time spent by children in the ED [weighted mean difference (WMD) = -0.62 hours; 95% CI: -0.84 to -0.40 hours]. Holding chambers also resulted in lower pulse rates in children [WMD = -10.0% baseline; 95% CI: -14.13% to -5.87% baseline].

Conclusions: Metered-dose inhalers with holding chamber produce outcomes that were at least equivalent to nebuliser delivery of beta-agonists in acute asthma. Uncertainty over delivery of equipotent doses from the different devices can be overcome by administering beta-agonists at short intervals (e.g. one respule via nebuliser or four separately inhaled actuations via a holding chamber every 15 to 20 minutes) with titration of number of treatments to the patient's response. The side effects in children may be more pronounced with nebulisers.

Citation: Cates C J. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

2 *ANTI-CHOLINERGIC DRUGS FOR WHEEZE IN CHILDREN UNDER THE AGE OF TWO YEARS*

Everard Mark L, Kurian Matthew.
Date of most recent substantive amendment: 28/05/1998.

Abstract

Objectives: To determine whether there is evidence to support the use of anti-cholinergic therapy in the treatment of wheezing infants.

Search strategy: The Cochrane Airways Group database which includes CINAHL, Embase and Medline, together with information from hand searching respiratory care and paediatric journals, was used. In addition personal contacts were made with colleagues and trialists working in the field of paediatric respiratory disease to identify other potentially relevant studies. Searches of the bibliography of the RCTs that had been found were undertaken. Boehringer Ingelheim and authors of identified trials were also contacted.

Selection criteria: Randomised controlled clinical trials involving wheezing infants and young children under the age of two years were included if patients received anticholinergic therapy. Due to the low numbers of trials and patients, studies that did not contain a placebo arm were included.

Studies including patients with 'acute bronchiolitis' (see text of review) and chronic lung disease of prematurity were excluded.

Data collection and analysis: All titles and abstracts identified by the search that appeared relevant were selected for full text review. Data extracted through review of results contained in papers was entered into the Cochrane Collaboration software program (Review Manager).

Main results:

- **Emergency Department Setting**.

The use of ipratropium bromide in the emergency department in addition to beta-agonists resulted in significantly fewer patients requiring further therapy 45 minutes after initial therapy compared with beta-agonist alone, in one study. However, in the other study in this setting, there was no difference in the frequency of a perceived 'excellent' response, change in respiratory rate or improvement in oxygen saturation when ipratropium was added to beta-agonist therapy.

- **Hospital Setting:** No significant reduction in duration of hospitalisation was identified in the single study comparing ipratropium alone versus placebo, and the addition of ipratropium to beta-agonist therapy had no effect on duration of hospitalisation compared with beta-agonist alone. Ipratropium plus beta-agonist therapy produced a significantly greater improvement in clinical score at 24 hours when compared to nebulised saline as placebo.

- **Home:** Maintenance treatment was perceived by parents to be preferable to nebulised water and better than placebo for the relief of symptoms.

Conclusions: The results do not support the uncritical use of anticholinergic for the treatment of wheeze in infancy. No clear benefit was identified from the use of anticholinergic agents in the emergency room or for the treatment of hospitalised infants. In the home setting parents were able to identify benefits compared with nebulised saline. Since these drugs are used for the relief of symptoms it is possible that the outcomes chosen in many of these studies were inappropriate and that a different choice of outcome measures may identify benefits in terms of symptom relief not evident from previous studies. Further work is required to clarify the exact role of anti-cholinergic agents in the treatment of wheeze in young children.

Citation: Everard Mark L, Kurian Matthew. Anti-cholinergic drugs for wheeze in children under the age of two years (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

3 *METHOTREXATE AS A STEROID SPARING AGENT IN ADULT ASTHMA*

Davies H, Olson L, Gibson P.
Date of most recent substantive amendment: 04/03/1998.

Abstract

Objectives: To conduct a systematic review of the literature concerning the benefit of adding MTX to oral corticosteroids in adults with stable asthma who were dependent on oral corticosteroids

Search strategy: An initial search was carried out via the Cochrane Airways Group Asthma RCT register. The search terms used for this review were steroid dependent OR methotrexate. Review articles and bibliographies identified from this process were surveyed for additional citations and RCTs. Trial authors were contacted for more information.

Selection criteria: Types of studies. All studies were randomised double-blind controlled trials in stable steroid-dependent adult asthmatics. All relevant studies were included. Studies in languages other than English were to be included.

Types of participants: Adult asthmatics requiring long term oral corticosteroids (OCS) for control of asthma. Trials in non-OCS dependent asthmatics, or in children (<16yo) were excluded.

Types of interventions: The addition of MTX or placebo in a blinded randomised fashion, by any route to therapy in adult steroid dependent asthmatic patients, with sufficient duration of therapy (at least 1 2weeks) to allow for any benefit from MTX to appear. Trials of inadequate duration (<12 weeks) were excluded.

Types of outcome measures: Study outcomes should have reported a wide range of measurements including alterations in steroid dosage.

Data collection and analysis: All identified RCTs were independently reviewed by two reviewers and all data collected. Reviews were scored according to the Cochrane assessment of allocation concealment and the Jadad scale of methodological quality. Disagreements between reviewers were referred to a third reviewer. Where further information was required, attempts were made to contact the authors of trial papers for further details and data.

Main results: A total of 13 RCTs were identified. Eleven were published studies and two were in abstract form only. Adequate data was available for analysis of 10 of the published studies. Of these, seven were cross-over studies and three were parallel studies. There were data for a total of 185 patients completing the trials. The patients in one large trial constituted of a third of the total. Study design, initial oral corticosteroid doses, inhaled corticosteroid use and reported outcomes varied widely.

Five studies found that the introduction of MTX to the treatment of chronic steroid-dependent asthmatics produced a significant decrease in dose of oral corticosteroids, whilst five found no such change. There were a significant number of side effects in the MTX treated patients. Meta-analysis was performed on parallel studies and cross-over studies separately. These

showed a reduction in oral corticosteroid dose (weighted mean difference) of -4.1 mg/day (95% CI -6.8, -1.3) favouring MTX in parallel trials; and a WMD of -2.9 mg/day (95% CI -5.5, -0.2) favouring MTX in cross-over trials. There was no difference in FEV_1, with a WMD of 0.12 L (95% CI -0.21, 0.45). Side effects were common. Hepatotoxicity was a particular problem with MTX, (Peto OR 6.9; 95% CI 3.1, 15.5) & was responsible for five of 32 withdrawals.

Conclusions: Methotrexate appeared to have a small steroid sparing effect in adult asthmatics who were dependent upon chronic oral corticosteroid therapy. The effect was relatively modest in most patients and accompanied by a significant number of side effects, most notably a degree of hepatotoxicity. The results of the ten studies reviewed here are varied. Most have a number of methodological flaws, including small numbers and inadequately described randomisation methods. The duration of many of these trials may have been insufficient to allow the full benefit of methotrexate to become apparent. Furthermore, evidence of inadequate or unstated inhaled corticosteroid usage, lack of a stable baseline oral corticosteroid dose during the run-in period and absence of a formal attempt to reduce this dose prior to the trial would suggest that other steroid-sparing stratagems may not have been employed optimally before introducing methotrexate. There is also evidence that supervision of the patients was closer than would be expected in non-trial conditions. It is possible that results seen in those trials where there was a significant reduction in oral steroid dose in both placebo and methotrexate treated patients was due to the improved supervision and overall management of the subject's asthma. It is not possible to conclude what effects these factors would have had on the magnitude of effect due to methotrexate. The overall reduction in daily steroid dose was probably too small to have reduced steroid-induced side-effects sufficiently to offset the increase in side-effects due to methotrexate. There was no improvement in airways function. The one death that occurred may have been associated with methotrexate use. There appears to be no case for the routine use of methotrexate in patients on long term oral steroids. In those patients for whom it may be considered, a very careful analysis of individual risk-benefit is required. There is a need for further studies into the effects of MTX on chronic steroid-dependent asthmatics.

Citation: Davies H, Olson L, Gibson P. Methotrexate as a steroid sparing agent in adult asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

4 *LONG-ACTING BETA-AGONISTS VERSUS THEOPHYLLINE FOR MAINTENANCE TREATMENT OF ASTHMA*

Wilson A, Gibson P, Coughlan JL.
Date of most recent substantive amendment: 12/2/1999.

Abstract

Objectives: To assess the comparative efficacy and safety of long-acting beta-agonists and theophylline in the maintenance treatment of asthma.

Search Strategy: Suitable randomised controlled trials (RCTs) were identified using the Cochrane Airways Group Database. The database was searched using the following terms: asthma and theophylline and long acting beta-agonist or formoterol or foradile or eformoterol or salmeterol or bambuterol or bilolterol. Titles and abstracts were then screened to identify potentially relevant studies. The bibliography of each RCT was searched for additional RCTs. Authors of identified RCTs were contacted for other relevant published and unpublished studies.

Selection Criteria: All included studies were RCTs involving adults and children with clinical evidence of asthma. These studies must have examined intervention with an inhaled long-acting beta-agonist: salmeterol; formoterol; eformoterol; bambuterol; bitolterol, versus ingested sustained release and/or dose adjusted theophylline.

Data Collection and Analysis: Potentially relevant trials identified by screening titles/abstracts were obtained. Two reviewers independently assessed full text versions of these trials for inclusion in the review and also assessed the methodological quality of the included trials, with particular emphasis on the allocation concealment that was ranked using the Cochrane approach. The quality scale of Jadad was also used. Where there was a disagreement between reviewers, this was resolved by consensus, or reference to a third party. Data was extracted using specially designed data extraction forms, by two independent reviewers. Inter-rater reliability was assessed by simple agreement. These comparisons were performed for each outcome. The study authors were contacted to clarify the randomisation method used, provide missing data, verify the data extracted, and identify any unpublished studies. Relevant pharmaceutical manufacturers were also contacted to obtain relevant information and unpublished studies. Outcome data was entered onto RevMan for statistical analysis. Categorical outcomes were assessed as risk reduction and 95% confidence intervals. Continuous outcomes were analysed as effect sizes with weighted or standardised mean difference as appropriate. Fixed effect models were used to obtain summary statistics for overall efficacy. Heterogeneity of results was assessed using a Chi-squared test.

Main Results: Theophylline versus a long-acting beta-agonist was reviewed in 6 RCTs of varying quality, conducted over a period of 8 years. There was a trend for salmeterol to improve FEV_1 more than theophylline (3 studies). More symptom free nights also tended to occur with salmeterol. Biltolterol (1 study) was less efficacious than theophylline. Participants taking salmeterol experienced fewer adverse events than those using theophylline (RR 0.38;95%CI 0.25,0.57). Significant reductions were reported for central nervous system

adverse events (RR 0.51;95%CI 0.30, 0.88) and gastrointestinal adverse events (RR 0.32;95%CI 0.17, 0.59).

Conclusion: Salmeterol may be more effective than theophylline in reducing asthma symptoms, including night waking and the need for rescue medication. More adverse events occurred in participants using theophylline when compared to salmeterol.

Citation: Wilson A, Gibson P, Coughlan J. Long acting beta-agonists versus theophylline (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

Critically Appraised Recommendations

1 **Does addition of long-acting beta-agonists to inhaled steroids in adult patients with mild-to-moderate asthma lead to better outcomes than management with inhaled steroids alone?**

Recommendation: *A long-acting beta-agonist may be considered in moderate asthma in addition to inhaled corticosteroids.*

Question: *Does the initiation of a long-acting beta-agonist in patients already on inhaled steroids result in better outcomes for adults with mild to moderate asthma?*

Answer: The addition of eformoterol to inhaled steroids in adult patients with mild-to-moderate asthma leads to a better outcome than management with inhaled steroids alone.

Search Strategy: A Medline search from 1966 to April 1998, using the term asthma, limiting the search to randomised controlled trials (RCTs).

Methods: Thirty-eight abstracts of RCTs were retrieved. The abstracts were reviewed and full text versions were retrieved if the study investigated the treatment of adults who had mild-to-moderate asthma with regular doses of formoterol in a randomised controlled trial. Of these, two RCTs met the inclusion criteria.

Results:

Trial	Interventions	N	Age	Male %	Significant Outcomes
Pauwels RA (1997)	Daily Dose: 1.BUD 200µg + placebo 2. BUD 200µg + FORM 24µg 3. BUD 800µg + placebo 4. BUD 800µg + FORM 24µg Length of study – 12 months	852	18-70 years	49%	Mean FEV_1 (% predicted) for the treatment groups at the start of the run-in period was 75.8%. The addition of FORM decreased the incidence of both severe and mild exacerbations in both BUD groups. Rates of severe and mild exacerbations were lower among patients given the higher dose of BUD and for severe exacerbations the effect of the higher dose of BUD was significantly greater than the effect of FORM. The addition of FORM to BUD in all groups was associated with improvement in both day and night symptom scores and reduced day and night rescue medications.
Van der Molen (1997)	Daily Dose: 1. Variable ICS + FORM 48 µg 2. Variable ICS + placebo	239	Mean age 43 years	49%	Mean FEV_1 (% predicted) at the start of run=-n was 67%. The addition of FORM led to a significant reduction in total symptom score, higher morning and evening PEFR, an increase in FEV_1 and a reduction in day and night rescue medication. There was no difference between the groups in asthma exacerbations.

Comments/Limitations: The validity of this recommendation is based on the results of two studies only, both of which showed a reduction in symptoms and improvement in peak flows

and one of which showed a reduction in exacerbations following addition of eformoterol to inhaled corticosteroids. One study was of six months duration, the other twelve months duration, and no studies to date have exceeded this duration.

References:

1. Pauwels R, Lofdahl C, Postma D, Tattersfield A, O'Byrne P, Barnes P, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids. New England Journal of Medicine 1997;337:1405-11.
2. Van der Molen T, Postma DS, Turner MO, Jong BM, Malo JL, Chapman K, Grossman R, de Graff CS, Riemersma RA Sears MR. Effects of the long acting beta-agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. The Netherlands and Canadian Formoterol Study Investigators. Thorax 1997;52:535-9.

Prepared by

1 Dr. Peter Bremner 14 December, 1998
2 Prof Bill Musk 14 December, 1998

2 Theophylline versus long-acting beta-agonists

Recommendation: *Sustained-release preparations make theophylline useful for the treatment of nocturnal asthma. Long-acting beta-agonists are also effective for nocturnal asthma.*

Question: *What is the comparative efficacy and toxicity of long-acting beta-agonists and theophylline in maintenance treatment of asthma?*

Answer: Salmeterol appears more effective than theophylline in reducing asthma symptoms, including night waking, and the need for rescue medication. More adverse events occur in patients using theophylline when compared to salmeterol.

Search Strategy: A Medline search from 1966 to April 1998, using the terms asthma and theophylline and formoterol or foradile or eformoterol or salmeterol or long-acting beta-agonists, limited to English language, identified 23 papers. Of these, six randomised, controlled trials compared theophylline with long-acting beta-agonists.

Results:

Trial	Interventions	n	Age range	Male %	Significant Outcomes
Pollard SJ (1997)	Salmeterol (SML) aerosol 42 µg, extended-release theophylline (THEO) capsules (individual dosage established in run-in period), or placebo, twice daily for 12 weeks.	484	12-80 years	49	SML was more effective in improving PEF, reducing the morning /evening PEF differential, and in reducing night waking. There were no significant differences in FEV_1 between SML and THEO. The SML group had greater clinical improvement, less adverse events (AEs), higher patient satisfaction with medication and used less rescue medication
Selby C (1997)	SML 50 µg bd with individually dose-titrated, sustained release, oral THEO, over 2 weeks with crossover.	15	20-66 years	47	Quality of life was higher on SML Night waking was lower on SML. Sleep studies showed fewer microarousals on SML and fewer errors were made in the continuous attention test of visual vigilance.
Paggiaro PL (1996)	SML 50µg bd or dose-titrated, slow-release THEO capsules bd for 4 weeks.	189	17-78 years	56	Significant increase in days without rescue medication for SML compared to THEO. Incidence of GIT AEs was greater among THEO patients.
Muir JF (1992)	SML 50 µg bd or a combination of slow-release THEO 300mg and ketotifen 1mg PO, bd (TK) for 28 days with crossover.	96	17-70 years	49	SML is better than TK as regards symptom-free nights, rescue medication intake, and FEV_1 . More AEs occurred in the TK group.
Fjellbirkeland L (1994)	SML 50 µg or individually dose-titrated oral THEO, both twice daily over 2 weeks.	141	18-75 years	57	SML had higher morning and night PEF, less night waking, less need for rescue medication and lower symptom scores. There were more AEs in the THEO group.
Zwillich CW (1989)	Dose-titrated THEO or bitolterol (BITOL) 1.11mg TDS for 2 weeks with crossover.	26	17-47 years	58	FEV_1 was higher in THEO group. Oxyhemoglobin desaturation during sleep was less on THEO than BITOL. Subject perception of symptom control and sleep quality was better on THEO.

Comments/Limitations: Salmeterol was the only long-acting beta-agonist that has shown benefits over theophylline in a randomised controlled trial. Bitolterol (one study) was seen to be less efficacious than theophylline. Paggiaro showed decreased asthma symptoms and increased PEF using salmeterol but did not state whether these trends were significant in any way.

References:

1 Fjellbirkeland L, Gulsvik A, Palmer JBD. The efficacy and tolerability of inhaled salmeterol and individually dose-titrated, sustained-release theophylline in patients with reversible airways disease. Resp Med 1994;88:599-607.

2 Muir JF, Bertin D, French Multicentre Study Group. Salmeterol versus slow-release theophylline combined with ketotifen in nocturnal asthma: a multicentre trial. Eur Respir J 1992;5:1197-1200.

3 Paggiaro PL, Giannini D, Di Franco A, Testi R, on behalf of a European Study Group. Comparison of inhaled salmeterol and individually dose-titrated slow-release theophylline in patients with reversible airway obstruction. Eur Respir J 1996;9:1689-1695.

4 Pollard SJ, Sheldon LS, Yancey SW, Cox FM, Emmett A. Salmeterol versus theophylline in the treatment of asthma. Ann Allergy Asthma Immunol 1997;78:457-464.

5 Selby C, Engleman HM, Fitzpatrick MF, Sime PM, Mackay TW, Douglas NJ. Inhaled salmeterol or oral theophylline in nocturnal asthma. Am J Respir Crit Care Med 1997;155:104-108.

6 Zwillich CW, Neagley SR, Cicutto L, White DP, Martin RJ. Nocturnal asthma therapy: Inhaled bitolterol versus sustained-release theophylline. Am Rev Respir Dis 1989;139:470-474.

Prepared by

1. Amanda Wilson 23 June, 1998

Cochrane Systematic Reviews in Progress

1 A comparison of inhaled long acting beta-agonists against placebo treatment in stable chronic asthma
2 A comparison of regular treatment with long acting beta-agonists against regular daily treatment with short acting beta-agonists in chronic stable asthma
3 Addition of anti-leukotriene agents to inhaled corticosteroids for recurrent and/or chronic asthma
4 Azoles for allergic bronchopulmonary aspergillosis
5 Cyclosporin as a steroid sparing agent for asthma
6 Dietary salt reduction or exclusion for allergic asthma
7 Early glucocorticoid use for preventing exacerbations of asthma
8 Gold as a steroid sparing agent for asthma
9 Inhaled steroids for asthma in children: effects on linear growth
10 Inhaled versus oral steroids for adults with chronic asthma
11 Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children
12 Regular versus "as-needed" inhaled short acting beta-agonists for asthma
13 The effectiveness of inhaled beclomethasone at different doses
14 The effectiveness of inhaled beclomethasone in the treatment of chronic asthma
15 The effectiveness of inhaled beclomethasone versus inhaled budesonide in the treatment of chronic asthma
16 The effectiveness of inhaled budesonide at different doses
17 The effectiveness of inhaled budesonide in the treatment of chronic asthma
18 Troleandomycin as a steroid sparing agent for asthma
19 How soon can back-titration of inhaled steroids be undertaken (eg when symptoms are in remission and/or when maximal lung function (peak flow or spirometry) has been reached)?
20 How rapidly and at what dose decrements should back-titration of inhaled corticosteroids be undertaken in order to maintain good asthma control on minimum medication?

Research Questions

1 Does the instruction to rinse, gargle and spit reduce gastro-intestinal absorption of inhaled steroid?
2 Does the instruction to rinse, gargle and spit reduce the frequency or severity of oral candidiasis?
3 Does the instruction to rinse, gargle and spit reduce the frequency and severity of hoarseness and dysphonia?
4 Early Intervention: At what level or frequency of symptoms should preventive therapy for asthma be commenced in adults?
5 Does the initiation of preventive medication (ICS) result in a better outcome for adults with mild asthma?
6 Does the initiation of regular preventive medication (cromoglycate) result in a better outcome for adults with mild asthma?
7 Does the initiation of regular preventive medication (nedocromil) result in a better outcome for adults with mild asthma?
8 Does the initiation of regular preventive medication (theophylline) result in a better outcome for adults with mild asthma?
9 Does the initiation of regular preventive medication (salmeterol) result in better outcomes for adults with mild asthma?
10 Does the initiation of regular preventive medication (antihistamines) result in a better outcome for adults with mild asthma?
11 In children, should maintenance preventative medication be commenced for: a) infrequent severe attacks b) reversible airway obstruction without symptoms c) attacks occurring more than once every six to eight weeks of any severity?
12 What is the optimum definition of good asthma control, which must be achieved before undertaking back-titration of inhaled corticosteroids?
13 Does a simple treatment regimen with a single medication (as opposed to multiple medications) result in improved compliance?
14 Is there a dose response relationship for systemic side effects and complications from long-term inhaled corticosteroids?

STEP 5: DEVELOP AN ACTION PLAN

Cochrane Systematic Reviews

1 Self-management education and regular practitioner review for adults with asthma

Critically Appraised Recommendations

No Critically Appraised Recommendations have been conducted on this topic.

Cochrane Systematic Reviews in Progress

There are 2 Cochrane Systematic Reviews in progress.

Research Questions

No research questions have been identified for this step.

Cochrane Systematic Reviews

1 ***SELF-MANAGEMENT EDUCATION AND REGULAR PRACTITIONER REVIEW FOR ADULTS WITH ASTHMA***

Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ, Walters EH.
Date of most recent substantive amendment: 29/05/1998.

Abstract

Objectives: Aim: to conduct a systematic review of the literature to identify whether education of asthmatics in self-management and regular review by a health practitioner improves health outcomes in adults with asthma.

Search strategy: Studies were identified from the following sources: The Cochrane Airways Group register (derived from MEDLINE, EMBASE, CINAHL), hand searched respiratory journals and meeting abstracts. The register was searched using the following terms: (Asthma OR wheeze)* AND (education* OR self management OR self-management). These articles were obtained, and their bibliographic lists were hand searched for additional articles.

Selection criteria: Studies were independently assessed by two reviewers for inclusion. Randomised controlled trials (RCTs) which studied the effects of asthma self-management education on health outcomes in adults with asthma were included.

Data collection and analysis: Study quality was assessed and data extracted independently by 2 reviewers. Confirmation of study methods and data was sought from authors. Studies were sub-grouped and analysed according to whether the asthma education intervention involved:
1) regular medical review (as a part of the program or advised by the program)
2) self-monitoring (PEF or symptoms)
3) an individualised written action plan which indicated when and how to adjust medications according to asthma severity.
4) Optimal self-management which involved all of the above.

Main results: Self-management asthma education was studied in twenty-four RCTs. Twenty-two studies compared self-management education with usual care. Self-management education reduced hospitalisations (OR 0.57), emergency room visits (OR 0.72), unscheduled visits to the doctor (OR 0.57), days off work or school (OR 0.55) and nocturnal asthma (OR 0.53). Improvements in PEF were marginal (8.4 l/min). Non-significant improvements were seen in FEV_1. Sub-group analyses showed that optimal self-management yielded larger and more clinically significant effect sizes than treatments which did not include a written action plan. Three studies which compared peak expiratory flow self-management with symptoms self-management showed no differences between these two forms of treatment for hospitalisations and unscheduled visits to the doctor. However, emergency room visits were significantly reduced by peak flow-based plans in one study (Cowie, 1997) while in another study (Charlton, 1990), significantly fewer subjects in the symptom-based group required a course of oral corticosteroids. In five studies which compared subjects who managed their

asthma by self-adjustment of medications according to an individualised written plan with those whose medications were adjusted by the doctor, lung function data (FEV_1 and PEF) were significantly higher in the self-managed group.

Conclusions: Self-management education about asthma which involves self-monitoring by either PEF or symptoms, regular medical review and a written action plan, improves health outcomes for adults with asthma. There are major reductions in resource use and improvements in morbidity. Asthma education that allows patient adjustment of medications based on a written action plan is more efficacious than asthma self-management education which does not.

Citation: Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ, Walters EH. Self-management education and regular practitioner review for adults with asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

Critically Appraised Recommendations

No Critically Appraised Recommendations have been conducted on this topic.

Cochrane Systematic Reviews in Progress

1 Educational interventions for adults with asthma
2 Educational interventions for children with asthma

Research Questions

No research questions have been formulated for this topic.

STEP 6: EDUCATE AND REVIEW REGULARLY

Cochrane Systematic Reviews

1 Limited (information only) patient education programs for adults with asthma
2 Self-management education and regular practitioner review for adults with asthma

Critically Appraised Recommendations

No Critically Appraised Recommendations have been conducted on this topic.

Cochrane Systematic Reviews in Progress

There are 2 Cochrane Systematic Reviews in progress.

Research Questions

No research questions have been identified for this step.

Cochrane Systematic Reviews

1 *LIMITED (INFORMATION ONLY) PATIENT EDUCATION PROGRAMS FOR ADULTS WITH ASTHMA*

Gibson PG, Coughlan J, Wilson AJ, Hensley MJ, Abramson M, Bauman A, Walters EH.
Date of most recent substantive amendment: 13/11/1997.

Abstract

Objectives: To conduct a systematic overview of the literature in order to identify whether limited (information only) asthma education leads to improved health outcomes in adults with asthma.

Search strategy: Studies were identified from the following sources: Cochrane Airways Group's register derived from MEDLINE, EMBASE, CINAHL, hand searched respiratory journals and meeting abstracts. The register was searched using the following terms: (Asthma OR wheeze)* AND (education* OR self management OR self-management). These articles were obtained, and their bibliographic lists were hand searched for additional articles.

Selection criteria: Two reviewers independently assessed full text articles for inclusion based upon the following criteria: a) Types of trials: RCTs, controlled clinical trials. b) Types of participants: adults (>16 years old) with asthma (defined by doctor's diagnosis or objective criteria). c) Types of intervention: asthma education delivered to person (or group of people) with asthma (and not their doctor), which was limited to information transfer only. Interventions involving: self-monitoring, enhanced medical management and written action plans were excluded. These will be subjects of a separate review. d) Types of outcomes: asthma admissions, emergency room visits, doctor visits, use of rescue beta-agonists, quality of life, lung function and symptom scores.

Data collection and analysis: Study quality was assessed and data extracted independently by 2 reviewers. Outcomes were analysed as continuous and dichotomous outcomes, using standard statistical techniques.

Main results: Limited asthma education was studied in 11 RCTs conducted over a period of 20 years, and with results reported of variable quality. Limited asthma education did not reduce hospitalisation for asthma and unscheduled doctor visits, and did not improve lung function. The effects on asthma symptoms were variable. There was no reduction in days lost from normal activity but perceived asthma symptoms did improve after limited asthma education. In the emergency department setting where adults have severe asthma and a high rate of re-attendance, limited asthma education did reduce ER attendance.

Conclusions: Health outcomes in adults with asthma are unlikely to be improved by the widespread use of limited asthma education as it has been practiced. Selective application of this intervention in the ER department setting looks promising.

Citation: Gibson PG, Coughlan J, Wilson AJ, Hensley MJ, Abramson M, Bauman A, Walters EH. Limited (information only) patient education programs for adults with asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

2 *SELF-MANAGEMENT EDUCATION AND REGULAR PRACTITIONER REVIEW FOR ADULTS WITH ASTHMA*

Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ, Walters EH.

Date of most recent substantive amendment: 29/05/1998.

Abstract

Objectives: Aim: to conduct a systematic review of the literature to identify whether education of asthmatics in self-management and regular review by a health practitioner improves health outcomes in adults with asthma.

Search strategy: Studies were identified from the following sources: The Cochrane Airways Group register (derived from MEDLINE, EMBASE, CINAHL), hand searched respiratory journals and meeting abstracts. The register was searched using the following terms: (Asthma OR wheeze)* AND (education* OR self management OR self-management). These articles were obtained, and their bibliographic lists were hand searched for additional articles.

Selection criteria: Studies from the above sources were independently assessed by two reviewers for inclusion. Randomised controlled trial (RCTs) which studied the effects of asthma self-management education on health outcomes in adults with asthma were included.

Data collection and analysis: Study quality was assessed and data extracted independently by 2 reviewers. Confirmation of study methods and data was sought from authors. Studies were sub-grouped and analysed according to whether the asthma education intervention involved:

1) regular medical review (as a part of the program or advised by the program)
2) self-monitoring (PEF or symptoms)
3) an individualised written action plan which indicated when and how to adjust medications according to asthma severity.
4) Optimal self-management which involved all of the above.

Main results: Self-management asthma education was studied in twenty-four RCTs. Twenty-two studies compared self-management education with usual care. Self-management education reduced hospitalisations (OR 0.57), emergency room visits (OR 0.72), unscheduled visits to the doctor (OR 0.57), days off work or school (OR 0.55) and nocturnal asthma (OR 0.53). Improvements in PEF were marginal (8.4 l/min). Non-significant improvements were seen in FEV_1. Sub-group analyses showed that optimal self-management yielded larger and more clinically significant effect sizes than treatments which did not include a written action plan. Three studies comparing peak expiratory flow self-management with symptoms self-management showed no differences between these two forms of treatment for hospitalisations and unscheduled visits to the doctor. However, emergency room visits were significantly reduced by peak flow-based plans in one study (Cowie, 1997) while in another study (Charlton, 1990), significantly fewer subjects in the symptom-based group required a course of oral corticosteroids. In five studies which compared subjects who managed their asthma by

self-adjustment of medications according to an individualised written plan with those whose medications were adjusted by the doctor, lung function data (FEV_1 and PEF) were significantly higher in the self managed group.

Conclusions: Self-management education about asthma which involves self-monitoring by either PEF or symptoms, regular medical review and a written action plan, improves health outcomes for adults with asthma. There are major reductions in resource use and improvements in morbidity. Asthma education that allows patient adjustment of medications based on a written action plan is more efficacious than asthma self-management education which does not.

Citation: Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ, Walters EH. Self-management education and regular practitioner review for adults with asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

Critically Appraised Recommendations

No Critically Appraised Recommendations have been conducted on this topic.

Cochrane Systematic Reviews in Progress

1 Educational interventions for adults with asthma
2 Educational interventions for children with asthma

Research Questions

No research questions have been formulated for this topic.

ALTERNATIVES TO PHARMACOTHERAPY:

Cochrane Systematic Reviews

1 The effect of physical training on asthmatic subjects
2 Acupuncture for chronic asthma
3 Family therapy for asthma in children
4 Do homeopathic treatments reduce the severity of asthma?
5 Speleotherapy for the treatment of asthma

Critically Appraised Recommendations

No Critically Appraised Recommendations have been conducted on this topic.

Cochrane Systematic Reviews in Progress

There are six Cochrane Systematic Reviews in progress.

Research Questions

Six research questions have been identified for this step.

Cochrane Systematic Reviews

1 *THE EFFECT OF PHYSICAL TRAINING ON ASTHMATIC SUBJECTS*

Ram FSF, Robinson SM, Black PN.
Date of most recent substantive amendment: 11/09/1998.

Abstract

Objectives: The purpose of this review was to assess the evidence from controlled clinical trials of the efficacy and effectiveness of physical training in the management of bronchial asthma.

Search strategy: The Cochrane Collaboration, Asthma and Wheeze randomised controlled clinical trials register was searched for studies. Separate additional searches were carried out on Medline (1966-1998), EMBASE (1980-1998), Sportdiscus (1949-1998) and also on the current contents index (1995-1998) as well as science citation index (1995-1998). the following terms were used to search for studies: asthma* and (work capacity OR physical activity OR training OR rehabilitation OR physical fitness). All searches were confined to human studies. The reference lists of all included studies were reviewed to identify trials not captured by electronic searches. Citations were reviewed without language restriction. Where additional data was required these were requested by writing to the authors of the study.

Selection criteria: Only RCTs of asthmatic subjects undertaking physical training were included. Subjects had to be 8 years and older, with asthma of any degree of severity. Physical training had to be undertaken for at least 20 to 30 minutes, 2 to 3 times a week, over a minimum of four weeks.

Data collection and analysis: Data abstraction of descriptive characteristics and study results was performed independently by two reviewers. If data were not reported in abstractable form, the authors were contacted for additional information. If the authors could not be contacted or if they were unable to provide the information, this was reported. Disagreements between the reviewers were resolved by consensus. Further information was sought from 7 authors whose trials were included in the review but only 2 responded. We did not write to authors of the 9 excluded trials since this would not have resulted in any of these studies being included. There were insufficient studies to allow analysis according to age of participants, type, intensity and duration of exercise training and control group intervention.

Main results: Independent review (by two reviewers FR and SR) of potentially relevant articles resulted in 8 studies being included in this review. In the results listed below, the figures in parenthesis indicate the number of studies that reported that particular outcome: Physical training had no effect on: PEFR (1), FEV_1 (2), FVC (1) and VEmax (1). In contrast, physical training led to the following changes: VO2max (4) increased by 5 ml/kg/min ($p < 0.001$, 95% CI = 3.5; 6.9). Work Capacity (1) increased by 28 W (185 training vs 157 control with n = 10 in both groups, $p < 0.001$). HRmax (2) increased by 3 bpm ($p = 0.034$, 95% CI = 0.2; 5.8). Episodes of Wheeze (1), expressed as the number of days in which the subject reported wheeze, increased by 21 days (31 training versus 12 control with n = 12 in both groups, $p = 0.032$).

Conclusions: Interpretation was limited by the small number of studies and the small number of subjects included in studies. Nonetheless, an increase in global cardiorespiratory capacity was demonstrated with physical training, as reflected in the increase in VO2max. This increase is of a magnitude similar to that seen in non-asthmatics and represents a training effect. Physical training had no effect on indices of resting lung function. The frequency of wheeze was higher in the exercise group in the one study that reported this, possibly due exercise-induced broncho-constriction resulting from increased levels of exercise either in daily life or due to training. No conclusions can be drawn about effects of exercise training on asthma symptom scores, bronchodilator use or quality of life.

Citation: Ram FSF, Robinson SM, Black PN. The effect of physical training on asthmatic subjects (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

2 *ACUPUNCTURE FOR CHRONIC ASTHMA*

Linde K, Jobst K, Panton J.
Date of most recent substantive amendment: 21/10/1998.

Abstract

Objectives: To evaluate the effectiveness of acupuncture for the treatment of bronchial asthma.

Search strategy: The databases of the Cochrane Airways Group, the Cochrane Field for Complementary Medicine, and reference lists of published reviews were searched.

Selection criteria: RCTs of acupuncture for the treatment of asthma or asthma-like symptoms.

Data collection and analysis: Information on patients, methods, interventions, outcomes, and results was extracted using standard forms. Only a small proportion of the data reported was in a format that could be extracted and used for the currently available Cochrane database.

Main results: Seven trials could be included. None of the trials were directly comparable. Two suggested that the acupuncture strategies investigated were superior to dummy acupuncture. Five revealed no significant difference between treatment and sham groups. However, some studies used sham points that can be used for the treatment of asthma according to the principles of traditional Chinese medicine, and only one used individualised treatment strategies.

Conclusions: It is not yet possible to make any recommendations to patients, their physicians or acupuncturists about the practice of acupuncture in the treatment of asthma on the basis of the data currently reported. Given the increasing use of acupuncture by the public, there is an urgent need for quality research that should take into account the complex nature of acupuncture as a treatment modality.

Citation: Linde K, Jobst K, Panton J. Acupuncture for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

3 ***FAMILY THERAPY FOR ASTHMA IN CHILDREN***

Panton J, White EA.
Date of most recent substantive amendment: 03/09/1996.

Abstract

Objectives: The purpose of the present review was to test whether family therapy as an adjuct to traditional medication can be shown to have a significant effect in reducing the symptoms and impact of asthma in children.

Search strategy: The Cochrane Airways Group has developed an 'Asthma and Wheez* RCT' database through a comprehensive search of Embase, Medline and CINAHL. In addition, the Psychlit database was searched. Searches of these databases have been completed using the following terms: The Airways Group databases combine Embase, CINAHL and Medline records. The Embase records identified through keyword or textword (in title, or abstract fields) searches on 'asthma*' or on the term 'wheez*'. In Medline and CINAHL the textword searches (in title, or abstract fields) are made on the terms 'asthma$' or 'wheez$'. The MeSH searches in Medline and CINAHL are made on the following two MeSH terms: 'respiratory sounds' and 'asthma'. The Medline records cover the period 1966 to present, Embase records span 1980 to present and the earliest CINAHL records date from 1982. The main Airways Group databases include the records downloaded from these three electronic systems. Searches are made in the main Airways Group databases on the following terms: 'placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study'. Those records are then exported to a separate RCT register.

For this review searches were made in the Airways Group asthma and wheez* RCT databases on: '(psycho* AND compliance) OR (cognit* AND therap*) OR (psychotherap*) OR (family therap*)'.

In addition to the Embase, CINAHL and Medline searches outlined above, extensive searches were made in a fourth electronic register: PsycInfo. The interface on this database allows psychological subject heading (SH) and text word (tw) searching, similar to Medline and CINAHL searching. These searches were:1 (asthma [SH] OR asthma$ [tw] OR wheez$ [tw]) AND family therapy [SH] 2 ((psychotherapeutic techniques [SH] OR psychotherapy [SH] OR child psychotherapy [SH] OR adolescent psychotherapy [SH] OR cognitive techniques [SH] OR personal therapy [SH] OR therapeutic processes [SH] OR counselling [SH] OR dysfunctional family [SH]) AND (asthma [SH] OR asthma$ OR wheez$)) AND NOT family therapy [SH] 3 ((family [tw] AND therap$ [tw]) AND (asthma [SH] OR asthma$ [tw] OR wheez$ [tw])) AND NOT family therapy [SH]

Selection criteria: OUTCOMES: Lung function; clinical assessments; subjective reports of symptoms and medication use. **DATA SOURCES:** Randomised controlled trials identified using the Cochrane Airways Group database. **STUDY SELECTION:** Twenty-four studies were identified in this area. Only two were RCTs. A maximum of 55 children was studied in these 2 RCTs, although most comparisons did not include all children initially enrolled.

Data collection and analysis: Data from the two studies could not be combined since different levels of data were presented.

Main results: Lung function: no significant difference was found between the groups in either peak expiratory flow rate (PEFR) or Forced Expiratory Volume in 0.75 seconds. However, one study (Lask & Matthews, 1979) found an improvement in Thoracic Gas Volume in family therapy patients compared with controls and a post family therapy improvement in PEFR within the experimental group. Clinical assessment: In one study (Gustaffson et al, 1986), improvement in family therapy patients was greater than in controls. Symptoms: Improvements were found in the number of functionally impaired days (Gustaffson et al, 1986) and in the amount of day wheeze (Lask & Matthew, 1979) for family therapy patients. Medication use: No difference was found between the groups.

Conclusions: Some support has been demonstrated for the use of family therapy as an adjunct to medication in the treatment of childhood asthma. However, current evidence comes from only two RCTs. Further, the strength of this evidence is limited by the use of small samples, missing data and unstandardised outcome measures. These methodological limitations and restrictions make it difficult to draw conclusions which are generalisable to a wider population. More, well designed, RCTs are needed to confirm the usefulness of family therapy in childhood asthma.

Citation: Panton J, White EA. Family therapy for asthma in children (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

4 *DO HOMEOPATHIC TREATMENTS REDUCE THE SEVERITY OF ASTHMA?*

Linde K, Jobst KA.
Date of most recent substantive amendment: 21/10/1998.

Abstract

Objectives: To evaluate the evidence for the effectiveness of homeopathic remedies, for the treatment of patients with stable chronic asthma.

Search Strategy: The databases of the Cochrane Airways Group, the Cochrane Field of Complementary Medicine, of the Glasgow Homeopathic Hospital and of the Munchener Modell were searched. The bibliographies of articles identified were checked for further trials.

Selection Criteria: RCTs of homeopathic remedies for the treatment of asthma.

Data Collection and analysis: Information on patients, methods, interventions, outcomes and results was extracted using standard forms.

Main Results: 3 trials met the inclusion criteria. All were placebo-controlled, randomised and double-blind, but they differed considerably regarding patient included, interventions used (3 different homeopathic remedies) and methodological quality, thus precluding quantitative meta-analysis. Two trials reported statistically significant positive outcomes for the tested homeopathic remedies compared with placebo and in the other trial no significant differences were observed.

Conclusions: The currently available evidence is insufficient to assess possible role of homeopathy in the treatment of asthma. The interventions investigated in the trials identified are unlikely to be representative of routine homoeopathic prescribing for the treatment of asthma in routine clinical practice. In general such treatment is likely to use individualised prescribing rather than remedies chosen for a disease entity such as asthma. Apart from RCTs there is a need for observational data to document the different methods and extent of homeopathic prescribing and how patients respond.

Citation: Linde K, Jobst KA. Homeopathy for chronic asthma. (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

5 ***SPELEOTHERAPY FOR THE TREATMENT OF ASTHMA***

Beamon S, Falkenbach A, Fairburg G, Linda K.
Date of most recent substantive amendment: 24/03/1999.

Abstract

Objective: The objective was to investigate whether there is evidence for the effectiveness of speleotherapy intervention in the treatment of asthma.

Search Strategy: We searched electronic databases (Medline, Embase, Cochrane Airways group database), connected speleotherapy centres and experts in the field, handsearched proceedings, and checked bibliographies of articles obtained to identify possible relevant publications.

Selection Criteria: We included controlled clinical trials (i.e. both randomised and those not reporting the method of allocation) that compared clinical effects of speleotherapy with another intervention or no intervention in patients with chronic asthma.

Data Collection and Analysis: Information concerning patients, interventions, results and methodology were extracted in standardised manner by two independent reviewers and summarised descriptively.

Main Results: Three trials including a total of 124 asthmatic children met the inclusion criteria. Only one trial had reasonable methodological quality. Two trials reported that speleotherapy had a beneficial short-term effect on lung function. Other outcomes could not be assessed in a reliable manner.

Conclusions: The available evidence does not permit a reliable conclusion as to whether speleotherapeutic interventions are effective f or the treatment of chronic asthma. Pragmatic randomised controlled trials with long-term follow-up are necessary.

Citation: Beamon S, Falkenbach A, Fairburg G, Linde K. Speleotherapy for the treatment of asthma. (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software

Critically Appraised Recommendations:

No Critically Appraised Reviews have been conducted on this topic.

Cochrane Systematic Reviews in Progress:

1 Does manual therapy reduce the severity of asthma?
2 Does the Alexander technique reduce the severity of asthma?
3 Does breathing training reduce the severity of asthma?
4 Dietary marine fatty acids for asthma
5 Vitamin C supplementation for asthma

Research Questions

1 Does control of sleep disordered breathing reduce the severity of asthma?
2 Does control of obstructive sleep apnoea reduce the severity of asthma?

ACUTE ASTHMA

We did not systematically define questions or conduct searches for management of acute asthma. The Cochrane Database of Systematic Reviews was searched for reviews pertaining to acute asthma.

Cochrane Systematic Reviews

1 Combined inhaled anticholinergics and beta-agonists for initial treatment of acute paediatric asthma
2 Corticosteroids for preventing relapse following acute exacerbations of asthma
3 Holding chambers versus nebulisers for beta-agonist treatment of acute asthma

Critically Appraised Recommendations

No Critically Appraised Recommendations have been conducted on this topic.

Cochrane Systematic Reviews in Progress

There are 11 Cochrane Systematic Reviews in progress.

Research Questions

No research questions have been identified for this step.

Cochrane Systematic Reviews

1 COMBINED INHALED ANTICHOLINERGICS AND BETA-AGONISTS FOR INITIAL TREATMENT OF ACUTE PAEDIATRIC ASTHMA

Plotnick LH, Ducharme FM.
Date of most recent substantive amendment: 28/02/1997.

Abstract

Objectives: The aims of this study were to estimate the magnitude of therapeutic effects and to describe the profile of adverse effects attributable to the addition of inhaled anticholinergics to beta-agonists in acute pediatric asthma.

Search strategy: We identified randomised controlled trials (RCTs) through (1) systematic literature searches of Medline(1966 to 1996), EMBASE (1980 to 1995) and CINAHL (1982 to 1995), (2) reference lists from identified RCTs, (3) correspondence with the pharmaceutical company producing ipratropium bromide, and (4) personal contact with colleagues and trialists.

Selection criteria: Randomised controlled trials comparing the combination of inhaled anticholinergics and beta-agonists with beta-agonists alone in children aged 18 months to 17 years with acute asthma were considered for inclusion.

Data collection and analysis: Relevant trials were independently evaluated by each reviewer for methodological quality and data extraction; confirmation of methodology and data was obtained from authors when possible. The primary endpoint was the hospital admission. The following secondary endpoints were also considered: pulmonary function tests (PFTs), clinical score, oxygen saturation (O_2 Sat), need for corticosteroids, number of treatments required after the protocol and prior to patient disposition, relapse to additional care and adverse effects.

Main results: Of the 37 identified studies, 10 RCTs were relevant and most (N=8) were of high quality. Studies were categorised according to the number of anticholinergic inhalations added to the beta-agonist regimen; one study tested two protocols. In single dose protocols (N=5), no reduction in hospital admission attributable to combination therapy was observed [OR=0.8 (99%CI:0.3,2.4), N=2]. However, significant group differences in the % change in FEV_1 were observed 60 minutes [WMD=16 (2,30)%, N=2] and 120 minutes [WMD=17 (4,15)%, N=2] after the combined anticholinergic and beta-agonist inhalation, both favouring combination therapy. No significant differences were observed in the other PFTs or other outcomes. In multiple dose protocols (N=5) which focused on severe exacerbations, a reduction in hospital admission rate was observed favouring combination therapy [OR=0.6 (0.3,1.1), N=5]. Eleven patients would need to be treated to avoid one admission. A 10 (4,15)% group difference in the change in % predicted FEV_1 favouring combination therapy was also noted 60 minutes after the last combined inhalation. No difference was observed in other outcomes. In the protocol titrating the number of combined anticholinergic and beta-agonist inhalations to patients' response (N=1), no group differences were observed for the few available outcomes.

Conclusions: The addition of a single inhalation of anticholinergics to the beta-agonist regimen may improve lung function without notable effect on hospital admission. Multiple dose protocols improve lung function and may avoid hospital admission in 1 of 11 such treated patients. These results seem to apply to children with moderate and severe asthma exacerbations. The protocol titrating the number of combined inhalations to clinical response did not appear to reduce the number of treatments required by patients. We were unable to satisfactorily examine how baseline severity and co-intervention with corticosteroids may influence these conclusions. The addition of anticholinergics to beta-agonists did not increase the amount of nausea, vomiting or tremor experienced by patients treated with any of the above three protocols.

Citation: Plotnick LH, Ducharme FM. Combined inhaled anticholinergics and beta-agonists for initial treatment of acute paediatric asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

2 CORTICOSTEROIDS FOR PREVENTING RELAPSE FOLLOWING ACUTE EXACERBATIONS OF ASTHMA

Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA , Bota GW.
Date of most recent substantive amendment : 26/05/1997.

Abstract

Objectives: To determine the benefit of corticosteroids (oral, intramuscular, or intravenous) for the treatment of asthmatic patients discharged from an acute care setting (i.e., usually the emergency department) after assessment and treatment of an acute asthmatic exacerbation.

Search strategy: The Cochrane Airways Group 'Asthma and Wheez* RCT' register was searched using the terms: a) Asthma OR Wheez* b) Glucocorticoid OR Steroid* AND c) Exacerbat* OR Relapse* OR Emerg*. In addition, authors of all included studies were contacted to determine if unpublished studies which met the inclusion criteria were available. Bibliographies from included studies, known reviews and texts were also searched for additional citations.

Selection criteria: Only randomised controlled trials were eligible for selection. Studies were included in this review if they dealt with the outpatient treatment of asthmatic exacerbations using glucocorticoids at discharge and reported either relapse rate or PFTs. Two independent reviewers first identified potentially relevant studies and then selected articles for inclusion. Methodological quality was assessed independently by two reviewers. Agreement was assessed using kappa (k) statistics.

Data collection and analysis: Data were extracted independently by two reviewers; authors were contacted to verify the extracted data and clarify missing information. When author contact was unsuccessful, missing data were estimated from graphs where possible. Sensitivity, sub-group and overall analyses were performed using the Cochrane Review Manager 3.0.

Main results: A search that yielded 229 references identified 169 (73%) original publications. Reviewers identified 8 studies for potential inclusion (k =0.76); 18 references were added by searching publication reference lists and contact with authors. Of these 26 articles, a total of 7 were included in the overview. Two studies used intramuscular corticosteroids, five studies used oral corticosteroids.

Significantly fewer patients in the corticosteroid group relapsed to receive additional care in the first week (odds ratio (OR) = 0.35; 95% confidence interval (CI): 0.17, 0.73). This favourable effect was maintained over the first 21 days (OR=0.33, 95% CI:0.13, 0.82). Patients receiving corticosteroids had less need for beta-agonists (weighted mean difference (WMD) = -3.3 activations/day; 95% CI: -5.5, -1.0). Changes in pulmonary function tests (SMD=0.045; 95% CI: -0.47, 0.56) and side effects (SMD=0.03; 95% CI : -0.38, 0.44) in the first 7-10 days, while rarely reported, showed no differences between the treatment groups. Statistically significant heterogeneity was identified for the side effect results; all other outcomes were homogeneous. It appears that IM corticosteroids are similarly efficacious to a 7-10 day tapering course of oral agents. From these results, as few as 9 patients need to be treated to prevent relapse to additional care after an exacerbation of asthma.

Conclusions: A short course of corticosteroids following assessment for an acute exacerbation of asthma significantly reduces the number of relapses to additional care and decreases beta-agonist use without an apparent increase in side effects. Intramuscular corticosteroids appear as effective as oral agents.

Citation: Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

3 HOLDING CHAMBERS VERSUS NEBULISERS FOR BETA-AGONIST TREATMENT OF ACUTE ASTHMA

Cates C J.
Date of most recent substantive amendment: 13/02/1998.

Abstract

Objectives: The objective of this review was to compare holding chambers to wet nebulisation for the delivery of beta-agonists in the treatment of acute asthmatic exacerbations.

Search strategy: Randomised controlled trials were identified using the Cochrane Airways Review Group and the Cochrane Controlled Clinical Trials Registers.

Selection criteria: All randomised controlled trials (RCTs) involving adults and/or children (from 2 years of age), where beta-agonists delivery was compared using wet nebulisation and holding chambers. Outcome measures included: admission to hospital, duration in the emergency department (ED), change in respiratory rate, blood gases, pulse rate, tremor, symptom score and lung function. One reviewer selected potentially relevant articles. Methodological quality was independently assessed by a second reviewer. Kappa tests were performed for agreement between reviewers.

Data collection and analysis: Data extraction was performed by a single reviewer (CJC). Missing data, (e.g. standard deviation for changes in lung function) were obtained from authors or estimated. Sensitivity analyses were performed to determine the impact of including estimated results from other data in the papers. The data were analysed using Cochrane Review Manager 3.0. The results for adults and children have been analysed separately due to significant heterogeneity in the pooled results. Only the results from multiple treatment studies have been pooled to avoid confounding by differences in drug delivery to the airways in single treatment studies.

Main results: 112 abstracts were originally identified from the database; of these 44 were identified from their title, keywords, MESH headings and abstracts as potentially relevant and were selected for detailed examination of the full paper. This review is restricted to 12 articles which met the inclusion criteria. One further article has been published since the previous version of this review. Inclusion of this trial has not altered the conclusions of this review. No significant difference was found in hospital admission rate in either adults or children when the two delivery methods were compared. [Adults: odds ratio (OR) = 1.12; 95% confidence interval (CI): 0.45 to 2.76. Children OR = 0.71; 95% CI: 0.23 to 2.23.] Significant differences were demonstrated in other outcomes, with holding chambers resulting in less time spent by children in the ED [weighted mean difference (WMD) = -0.62 hours; 95% CI: -0.84 to -0.40 hours]. Holding chambers also resulted in lower pulse rates in children [WMD = -10.0% baseline; 95% CI: -14.13% to -5.87% baseline].

Conclusions: Metered-dose inhalers with holding chamber produce outcomes that were at least equivalent to nebuliser delivery of beta-agonists in acute asthma. Uncertainty over delivery of equipotent doses from the different devices can be overcome by administering beta-agonists at short intervals (e.g. one respule via nebuliser or four separately inhaled

actuations via a holding chamber every 15 to 20 minutes) with titration of number of treatments to the patient's response. The side effects in children may be more pronounced with nebulisers.

Citation: Cates C J. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

Critically Appraised Reviews

No Critically Appraised Reviews have been conducted on this topic.

Cochrane Reviews in Progress

1 Combined inhaled beta-agonist and anticholinergic agents for emergency management of adults in asthma
2 Continuous versus intermittent beta-agonists for treating acute asthma in the emergency department
3 Corticosteroids dosages for acute severe asthma requiring hospital admission
4 Inhaled bronchodilators for asthma in patients being mechanically ventilated
5 Inhaled corticosteroids for acute asthma
6 Interventions for educating children who have attended the emergency room for asthma
7 Intravenous aminophylline for acute asthma in adults
8 Intravenous aminophylline for acute severe asthma in children over 2 years using inhaled bronchodilators
9 Magnesium sulphate for asthmatic exacerbations
10 Oral steroids in the initial management of acute asthmatic exacerbations: prevention of hospital admissions
11 Parenteral adrenergic beta-agonists for exacerbations of asthma in the emergency setting

Research Questions

No research questions have been formulated for this topic.

THE QUESTIONS

Preamble

The methodology used to develop the questions is provided on page 12 of this report.

ID: The ID is the individual question identification number. The preceding numeral indicates the step to which the question relates. A '0' was used for questions relating to diagnosis which did not specifically relate to any section in the asthma management handbook.

Question: This column lists the questions that have been devised.

Status: This column categorises the questions according to whether or not they were able to be answered with level one evidence. The categories are as follows:
Not suitable – The question does not lend itself to study by randomised controlled trial.
Suitable – The question is suitable for examination by randomised controlled trial.
Cochrane Review Complete – this indicates that a Cochrane review is available to answer this question. If this is the case, the abstract will be available in the Results section of this book.
Cochrane Protocol – a Cochrane Protocol has been published on the Cochrane Database of Systematic Reviews.
Identified by a Cochrane Reviewer – this indicates that a Cochrane Reviewer has let the Cochrane Airways Group know that they will be submitting a Protocol in the near future on this topic. As such, these questions were not available for allocation.
CAR Completed by One or Two reviewers – a Critically Appraised Recommendation has been completed for this question (by one or two reviewers). The full CAR can be viewed in the Results section of this report.
Unsure – this indicates that the question has not been searched.
Question Redefined – indicates that the question was reformulated. This occurred for two reasons. The first to allow the question to be answered by the available literature: the second to reframe the question to more accurately reflect the recommendation.

RCTs: This column indicates if randomised controlled trials were available on a search of the literature.
"?" = unsure
"nil" = no randomised controlled trials found
"yes" = randomised controlled trials found. It should be noted however, that not all papers were assessed for inclusion/exclusion and as such, some questions may indicate that RCTs are available when the papers retrieved are not applicable to answering the question.

Page Number:
This report was based on the 1996 *Asthma Management Handbook*. The page number indicates the page on which the relevant comment or recommendation was made. The words "not mentioned" indicate that no relevant recommendation or comment could be found for that question.

Diagnosis				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	Can adult/childhood asthma be sub-grouped into different types according to their natural history?- lability of symptoms and lung function- average lung function	Not suitable	Nil	Not mentioned
2	If asthma can be subgrouped, do the various subgroups have different prognoses and responses to treatment?	Not suitable	Nil	Not mentioned
3	What is the sensitivity and specificity of a diagnosis made by a FEV_1 bronchodilator response of 15%?	Not suitable	?	Not mentioned
4	What is the effect on health outcomes of a doctor's diagnosis of asthma on episodic respiratory symptoms?	Not suitable	Nil	Not mentioned
5	What is the effect of a doctor's diagnosis of asthma on future management of asthma?	Not suitable	Nil	Not mentioned
6	What is the effect of a doctor's diagnosis of asthma on prognosis?	Not suitable	Nil	Not mentioned

Step 1 – Assess Asthma Severity				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	Is measuring severity necessary?	Not suitable	Nil	15
2	What is the relationship between lung function and symptom severity, eg if assessed as mild asthma?	Not suitable	Nil	15
3	Is there difference between severity (intensity) and the frequency of symptoms in the assessment of asthma severity?	Not suitable	Nil	?
4	Is there a role for regular preventer medications for patients who have infrequent episodic asthma (severe or viral)?	Not suitable	Nil	?
5	Does individualising treatment on the basis of severity lead to better outcomes?	Not suitable	?	15
6	Does assessing the severity of every patient and individualising treatment improve health outcomes?	Not suitable	Nil	15
7	What is the outcome for patients assessed and managed as high risk?	Not suitable	Nil	16
8	Does the assessment of asthma severity influence choice of therapy?	Not suitable	Nil	34-36
9	Does the assessment of asthma severity influence intensity of therapy?	Not suitable	Nil	34-36
10	Does the assessment of asthma severity influence outcome of therapy?	Not suitable	Nil	34-36
11	Does the assessment of asthma severity influence maintenance therapy requirements?	Not suitable	Nil	21-24
12	Does the presence of nocturnal asthma correlate with objective measures of asthma?	Not suitable	Nil	8
13	What is the sensitivity / specificity of work loss / missed school as markers of severity?	Unsure	?	15

Step 2 – Achieve Best Lung Function				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	In patients with and FEV_1 of at least 80% does treatment with an inhaled corticosteroid </=800 μg per day plus a beta-agonist as required improve asthma outcomes.	CAR completed by two	Yes	17
2	In patients with and FEV_1 of greater than 80% does treatment with an inhaled corticosteroid >800 μg per day plus a beta-agonist as required improve asthma outcomes.	CAR completed by two	Yes	17
3	In patients with and FEV_1 of less than 80% does treatment with an inhaled corticosteroid </=800 μg per day plus a beta-agonist as required improve asthma outcomes.	CAR completed by two	Yes	17
4	In patients with and FEV_1 of less than 80% does treatment with an inhaled corticosteroid >800 μg per day plus a beta-agonist as required improve asthma outcomes.	CAR completed by two	Yes	17
5	In patients with an unknown FEV_1 does treatment with an inhaled corticosteroid </=800 μg per day plus a beta-agonist as required improve asthma outcomes.	CAR completed by two	Yes	17
6	In patients with an unknown FEV_1 does treatment with an inhaled corticosteroid >800 μg per day plus a beta-agonist as required improve asthma outcomes.	CAR completed by two	Yes	17
7	Does improving lung function result in better health outcomes?	Not suitable	?	17
8	If aggressive initial treatment with inhaled steroids does not improve asthma control/achieve normal lung function does this mean that the diagnosis is wrong?	Unsure	?	17
9	If aggressive initial treatment with inhaled steroids does not improve asthma control / achieve normal lung function, if the diagnosis is right, is the prognosis poor?	Unsure	?	17
10	If aggressive initial treatment with inhaled steroids does not improve asthma control / achieve normal lung function and the diagnosis is right, will future management be difficult?	Not suitable	?	17
11	Do adults who have regular office spirometry have better health outcomes?	Suitable	?	17
12	Do children who have regular medical review have better health outcomes?	Suitable	?	17 & 31
13	Do adults who regularly measure PEF have better health outcomes?	Cochrane Review Complete	Yes	31
14	Do adults who regularly measure symptoms have better health outcomes?	Cochrane Review Complete	Yes	31
15	Do children who regularly measure symptoms have better health outcomes?	Suitable	?	31
16	Is there a correlation between office and home measurement of lung function?	Not suitable	?	?
17	Does the regular use of an electronic diary spirometer improve health outcomes?	Suitable	?	?
18	How should best lung function be achieved?	Not suitable	?	17
19	Does a step up approach to treatment, compared with higher	Unsure	?	23

	dose therapy improve health outcomes?			
20	Is best lung function achieve more often/more quickly in subjects with mild/moderate asthma (see table p15) who are treated with intensive therapy (1CS>750mg/d) versus sodium cromoglycate / nedocromil sodium?	Unsure	?	15 & 17
21	Is best lung function achieved more often / more quickly in subjects with severe asthma by the use of ICS 750-2000 mg/d or oral corticosteroids?	Unsure	?	17
22	Is asthma control/ symptom relief achieved more often / more rapidly in children with infrequent episodic asthma by the use of sodium cromoglycate / nedocromil sodium or inhaled corticosteroids.	Not suitable for a Cochrane Review	?	17
23	Is asthma control/ symptom relief achieved more often / more rapidly in children with frequent episodic asthma by the use of sodium cromoglycate / nedocromil sodium or inhaled corticosteroids.	Unsure	?	17
24	Is asthma control/ symptom relief achieved more often / more rapidly in children with persistent episodic asthma by the use of sodium cromoglycate / nedocromil sodium or inhaled corticosteroids.	Unsure	?	17

Step 3 – Maintain Best Lung Function				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	Allergens – What are the effects of allergen specific immunotherapy in asthma?	Cochrane Review Complete	Yes	not mentioned
2	Do patients instigate allergen avoidance procedures following the identification of specific sensitisation by means of skin tests, IgE or RAST measurements?	Not suitable	Nil	12, 18 and 61
3	Do patients instigate allergen avoidance procedures if advised to do so by their doctor?	Not	Nil	18
4	Does house dust-mite reduction have a beneficial effect on asthma?	Cochrane Review	Yes	18 & 67
5	Does allergen avoidance reduce the severity of asthma?	Suitable	Yes	18, 19, 20, 67
6	Does avoidance of ingested allergen prevent the development of atopy/asthma	CAR completed by 2 reviewers + Cochrane Review	Yes	18 & 67
7	Infections: What is the effect of influenza vaccination on asthma?	Cochrane Protocol	Yes	18
8	Does influenza increase the severity of asthma?	Not suitable	Nil	18
9	Does treatment with antibiotics during an exacerbation of asthma reduce the time course of the exacerbation?	CAR completed by 2 reviewers	Yes	18
10	Exercise: Does pre-exercise inhalation of nedocromil sodium attenuate exercise induced airway narrowing?	Cochrane Protocol	Yes	63
11	Does regular exercise reduce the severity of asthma?	Cochrane Review Complete	Yes	68
12	What is the effect of caffeine on asthma?	Cochrane Review Complete	Yes	not mentioned
13	Does tartrazine intake increase asthma exacerbations?	Cochrane Protocol	Yes	not mentioned
14	Does dietary cow's milk increase the severity of asthma?	Cochrane Protocol	Yes	19, 61
15	Does high salt intake increase the severity of asthma?	Cochrane Protocol	Yes	not mentioned
16	Does low anti-oxidant intake increase the severity of asthma	Suitable	?	not mentioned
17	What is the efficacy of vitamin C supplementation in the treatment of asthma	Cochrane Protocol	Yes	Not mentioned
18	Does low omega-6 fatty acid intake reduce the severity of asthma?	Cochrane Protocol	Yes	Not mentioned
19	Gastro-oesophageal reflux: Does treatment of gastro-oesophageal reflux (symptomatic and non-symptomatic) improve asthma control?	Cochrane Review Complete	Yes	19

Step 4 - Maintain Best Lung Function – Optimise Medication Program				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	How soon can back-titration of inhaled steroids be undertaken when symptoms are in remission and maximal lung function (peak flow or spirometry) has been reached?	Cochrane Protocol	Yes	21
2	What is the optimum definition of good asthma control, which must be achieved before undertaking back-titration of inhaled corticosteroids?	Identified by a Cochrane Reviewer	Yes	21
3	How rapidly and at what dose decrements should back-titration of inhaled corticosteroids be undertaken in order to maintain good asthma control on minimum medication?	Identified by a Cochrane Reviewer	Yes	21
4	Lung Function: What is the best method to achieve good asthma control - regular doctor adjusted medication or self-management?	Cochrane Review Complete	Yes	21
5	What is the best method of self-management to achieve good asthma control - PF or Symptoms?	Cochrane Review Complete	Yes	21
6	Exacerbations: What dose and duration of oral corticosteroids for the management of acute exacerbations ensures the most rapid and sustained recovery?	Identified by a Cochrane Reviewer	Yes	21
7	Side Effects: Is there a dose response relationship for inhaled corticosteroids with respect to local side effects and adverse events?	Identified by a Cochrane Reviewer	Yes	21
8	Is there a dose response relationship for systemic side effects and complications from long-term inhaled corticosteroids?	Identified by a Cochrane	Yes	21
9	Does the use of cromoglycate reduce side effects in children requiring regular preventive medication compared to inhaled corticosteroids?	Identified by a Cochrane Reviewer	Yes	21
10	Does a simple treatment regimen with a single medication (as opposed to multiple medications) result in improved compliance?	Suitable	?	21
11	Does the instruction to rinse, gargle and spit reduce gastro-intestinal absorption of inhaled steroid?	Identified by a Cochrane Reviewer	Yes	21
12	Does the instruction to rinse, gargle and spit reduce the frequency or severity of oral candidiasis?	Identified by a Cochrane Reviewer	Nil	21
13	Does the instruction to rinse, gargle and spit reduce the frequency and severity of hoarseness and dysphonia?	Identified by a Cochrane Reviewer	Nil	21
14	Early Intervention: At what level or frequency of symptoms should preventive therapy for asthma be commenced in adults?	Not suitable for a Cochrane Review	Yes	22
15	Does the initiation of preventive medication (ICS) result in a better outcome for adults with mild asthma?	Suitable	Yes	22
16	Does the initiation of regular preventive medication	Suitable	Yes	22

	(cromoglycate) result in a better outcome for adults with mild asthma?			
17	Does the initiation of regular preventive medication (nedocromil) result in a better outcome for adults with mild asthma?	Suitable	Yes	22
18	Does the initiation of regular preventive medication (theophylline) result in a better outcome for adults with mild asthma?	Suitable	Yes	22
19	Does the initiation of regular preventive medication (salmeterol) result in better outcomes for adults with mild asthma?	Question redefined	Yes	22
20	Does addition of salmeterol to inhaled steroids in adult patients with mild-to-moderate asthma lead to better outcomes than management with inhaled steroids alone?	CAR allocated to an expert reviewer	?	22
21	Does the initiation of regular preventive medication (formoteroll) result in better outcomes for adults with mild asthma?	Question redefined	Yes	22
22	Does addition of eformoterol to inhaled steroids in adult patients with mild-to-moderate asthma lead to better outcomes than management with inhaled steroids alone?	CAR completed by two reviewers	Yes	22
23	Does the initiation of regular preventive medication (antihistamines) result in a better outcome for adults with mild asthma?	Suitable	Yes	22
24	In children, should maintenance preventative medication be commenced for: a) infrequent severe attacks b) reversible airway obstruction without symptoms c) attacks occurring more than once every six to eight weeks of any severity?	Not suitable	?	25
25	Are puffer and spacer as effective as nebulisers for delivery of bronchodilators in the management of acute asthma exacerbations in adults and children?	Cochrane Review Complete	Yes	21
26	What is the comparative efficacy and toxicity of long acting beta-agonists and theophylline in maintenance treatment of moderate to severe asthma?	Cochrane Review Complete	Yes	45

Step 5 – Develop an Action Plan				
ID	**Question**	**Status**	**RCTs**	**Page Number**
5.1	Does a written action plan result in earlier recognition of deterioration by a person with asthma (compared to person without a written action plan)?	Suitable	Nil	28
5.1.1	Does the decision to call an ambulance and continue the use of reliever medication with a peak flow of <40% of best improve outcomes in adults with asthma?	Not suitable	?	28
5.2	Does a written action plan increase adherence to the recommended actions by a person with asthma (compared to a person without written action plan)?	Cochrane Protocol	?	28
5.3	Does a written action plan result in improved outcomes for a person with asthma (compared to a person without a written action plan)?	Cochrane Review Complete	Yes	28
5.4	Does earlier recognition of deterioration result in improved outcomes for a person with asthma (compared with late recognition of deterioration)?	Not suitable	?	28
5.5	Does a written action plan based on peak expiratory flows result in better outcomes for a person with asthma (compared to a symptom-based plan)?	Cochrane Review Complete	Yes	28
5.6	Does an individualised action plan result in better outcomes for a person with asthma (compared with a standardised plan)?	Suitable	Yes	28
5.7	What is the sensitivity and specificity of a cut-off peak flow 80% in identifying asthma attack in an adult?	Not suitable	Nil	28
5.8	Does the use of inhaled corticosteroids with a peak flow of 60-80% of best improve outcomes in adults with asthma?	Not suitable	?	28
5.9	Does the initiation or resumption of oral corticosteroids at a peak flow of 40-60% of best improve outcomes in adults with asthma?	Not suitable	?	28

Step 6 – Educate and Review Regularly				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	What are the effects of limited education (information only) patient education programs on adults?	Cochrane Review Complete	Yes	31
2	What is the effect of self-management education and regular review on asthma outcome in adults?	Cochrane Review Complete	Yes	31
3	What is the impact of asthma education on behavioural and health outcomes in children?	Cochrane Protocol	Yes	31
4	What is the effect of asthma education on health outcomes in children who have attended the emergency department?	Cochrane Protocol	Yes	31
5	What is the effect of asthma education on health outcomes in adults who have attended the emergency department?	Identified by a Cochrane Reviewer	Yes	31
6	What effect does provision of asthma education to health professionals have on people with asthma?	Cochrane Protocol	Yes	Not mentioned
7	What are the effects of training asthmatics in the use of inhalation devices?	Suitable	Yes	31

Exposure Series				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	Does exposure to SO_2 increase asthma severity/ exacerbations?	Question redefined	Yes	20
2	Does brief exposure to SO_2 under laboratory conditions with episodes of exercise, have an adverse effect on lung function in asthmatic subjects?	CAR completed by two reviewers	Yes	20
3	Does exposure to PM10 increase asthma severity/ exacerbations?	Not suitable	Nil	20
4	Does exposure to NOx increase asthma severity/ exacerbations?	Question redefined	Yes	20
5	Does brief exposure to NO_2 combined with exercise under laboratory conditions, alter lung function in subjects with asthma?	CAR completed by two reviewers	Yes	20
6	Does exposure to cold air increase asthma severity/ exacerbations?	CAR allocated to an expert reviewer	Yes	20
7	Does exposure to low levels of NO_2 increase the allergic response of adults with asthma?	Cochrane Protocol	Yes	20
8	Does brief exposure to NO_2 in combination with SO_2 under laboratory conditions increase airway hyperresponsiveness in asthmatic subjects?	CAR completed by two reviewers	Yes	17
9	Does brief exposure to NO_2 at rest under laboratory conditions increase allergen or methacholine-induced airway hyperresponsiveness in atopic asthmatic subjects?	CAR completed by two reviewers	Yes	20
10	Does exposure to environmental tobacco smoke increase asthma severity/ exacerbations?	Identified by a Cochrane Reviewer	?	20

Avoidance Series				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	Does avoidance of SO2 improve asthma/reduce severity/reduce exacerbations?	Not suitable	Nil	20
2	Does avoidance of PM10 improve asthma/reduce severity/reduce exacerbations?	Not suitable	Nil	20
3	Does avoidance of NOx improve asthma/reduce severity/reduce exacerbations?	Not suitable	Nil	20
4	Does avoidance of cold air improve asthma/reduce severity/reduce exacerbations?	Not suitable	Nil	20
5	What is the effect of air pollution on allergen induced asthma?	Not suitable	Yes	20
6	Does reduction of environmental tobacco smoke improve asthma control?	Identified by a Cochrane Reviewer	?	20
7	Does avoidance of non-sensitising occupational irritants improve asthma control?	Unsure	?	20
8	Does avoidance of non-sensitising occupational irritants reduce asthma severity?	Unsure	?	20
9	Does avoidance of non-sensitising occupational irritants reduce exacerbations?	Unsure	?	20
10	Does avoidance of domestic sensitisers improve asthma?	Unsure	?	20
11	Does avoidance of domestic sensitisers reduce asthma severity?	Unsure	?	20
12	Does avoidance of domestic sensitisers reduce asthma exacerbations?	Unsure	?	20
13	Does avoidance of occupational sensitisers improve asthma?	Unsure	?	20
14	Does avoidance of occupational sensitisers reduce asthma severity?	Not suitable	Nil	20
15	Does avoidance of occupational sensitisers reduce asthma exacerbations?	Unsure	?	Not mentioned
16	Temperature changes: Does sleeping in a warm room prevent nocturnal exacerbations of asthma?	Suitable	Nil	20

Alternatives to Pharmacotherapy				
ID	**Question**	**Status**	**RCTs**	**Page Number**
1	Does family therapy reduce asthma exacerbations?	Cochrane Review Complete	Yes	Not mentioned
2	Does acupuncture reduce the severity of asthma?	Cochrane Review Complete	Yes	Not mentioned
3	Do homoeopathic treatments reduce the severity of asthma?	Cochrane Review Complete	Yes	Not mentioned
4	Does manual therapy reduce the severity of asthma?	Cochrane Protocol	Yes	Not mentioned
5	Does the Alexander technique reduce the severity of asthma?	Cochrane Protocol	Yes	Not mentioned
6	Does breathing training reduce the severity of asthma?	Identified by a Cochrane Reviewer	Yes	Not mentioned
7	Does control of sleep-disordered breathing reduce the severity of asthma?	Suitable	?	Not mentioned
8	Does control of obstructive sleep apnoea reduce the severity of asthma?	Suitable	?	Not mentioned

Appendix I - Critically Appraised Recommendation - Protocol

For the Six Step Asthma Management Plan

What is a critically appraised recommendation (CAR)?

A CAR is a review of the randomised controlled trials which relate to a clinical question derived from a recommendation in the *Asthma Management Handbook*. This forms part of the NAC-NSW Health project that seeks to identify, grade and summarise the evidence behind the Six Step Asthma Management Plan.

The hierarchy of literature is as follows:

Level I	A meta-analysis of randomised controlled trials, or a single large trial
Level II	One or more randomised controlled trials
Level III	Controlled trials without randomisation (cohort studies, case-control studies, analytic studies, multi-time series, before and after studies (preferably from more than one centre or research group))
Level IV	Other observational studies
Level V	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

In the absence of a meta-analysis or Cochrane Systematic Review we will use a Critically Appraised Recommendation to answer questions about recommendations. This project is seeking to base its CARs on randomised controlled trials (i.e. identify recommendations which have Level II evidence).

How will it be used?

The CAR will be placed in a booklet (of other CARs and summaries of Cochrane Systematic Reviews) that will be available with the *Asthma Management Handbook*. The evidence-based review will be on the NAC or NSW Health Website, which is accessed by any interested person. The level of evidence supporting a recommendation will also be indicated in the *Asthma Management Handbook* to provide a quick gauge to guide confidence in that recommendation.

How to do a CAR

You will be sent the research question and a set of papers (including the search strategy) and a format to standardise the presentation of CARs. You may find Sackett et al's (1997) *Evidence-based Medicine: How to Practice and Teach EBM* published by Churchill Livingston useful. In summary you will need to:

1. Refine the question (if necessary) to clearly identify

- the population
- the treatment or intervention
- the outcomes
- the study design

2. Obtain reports of randomised controlled trials to answer the question:

- review the search strategy and improve it if necessary
- review the reference lists of papers provided to identify any missing papers
- obtain the missing papers and review their reference lists
- discard any studies that are not randomised or do not answer the question.

3. Use the example provided to document the salient features of each study in the standard tabulated format:

- first author and date of study (place studies in chronological order)
- intervention (summarise the key features of the treatment of the intervention group)
- number of subjects who participated and proportion completed
- proportion who were male /female
- outcomes, significant and not significant.

4. In the limitations/comments section: please note any obvious heterogeneity among the studies (ie differences in populations studied, setting, disease severity, ethnicity, socio-economic status etc) or among the study results. Note any outstanding methodological problems (eg baseline characteristics of intervention and control groups were obviously different; allocation to groups was not truly randomised or the methods used for randomisation were not stated; subjects were not assessed or data was not presented in their allocated groups; outcome assessors were not blinded; withdrawals were not explained).

5. Prepare a brief answer and place it in the highlighted 'answer box' at the top of the CAR.

6. Have another person also review independently the papers and prepare the CAR and compare your results. Discuss and resolve any differences.

7. Submit your CAR: to the steering committee who will undertake editorial review prior to publication in the Evidence-based review of the Six Step Asthma Management Plan.

N.B. The standard format can be provided to you on a disk, or via email if you choose, in Microsoft Word Version 6 format.

Relationship to the Cochrane Collaboration:

If you wish to register a title and convert your CAR into a systematic review, the title will need to be registered with and approved by the Cochrane Airways Group based at St George's, London. Publication of a Critically Appraised Recommendation in the Evidence-based review of the Six Step Asthma Management Plan does not guarantee ownership of that area in the Cochrane Collaboration.

If you or another person or group undertake a CAR which is also being undertaken as a Cochrane Systematic Review, if the Cochrane Review is completed and answers the question of your CAR, the CAR will be supplanted by the Cochrane Systematic Review.

How you will be acknowledged

If you complete a CAR, your name and the date of submission and acceptance will be published with the CAR. (e.g. prepared by ..., date)

What is the timeframe to complete the CAR?

It takes about an hour per paper to extract the required data and comment on methodological problems. While the timeframe varies according to the number of papers it is expected that any CAR could be completed within a 3-month period.

Australian Cochrane Centre: www.cochrane.org.au

Appendix II - A Critically Appraised Recommendation and a Subsequent Cochrane Systematic Review of the Same Recommendation

1 Recommendation:

Recommendation: *Sustained-release preparations make theophylline useful for the treatment of nocturnal asthma. Long-acting beta-agonists are also effective for nocturnal asthma.*

2 Critically Appraised Recommendation:

Theophylline versus long-acting β_2-agonists

Recommendation: *Sustained-release preparations make theophylline useful for the treatment of nocturnal asthma. Long-acting beta-agonists are also effective for nocturnal asthma.*

Question: *What is the comparative efficacy and toxicity of long acting beta-agonists and theophylline in maintenance treatment of asthma?*

Answer: Salmeterol appears more effective than theophylline in reducing asthma symptoms, including night waking, and the need for rescue medication. More adverse events occur in patients using theophylline when compared to salmeterol.

Search Strategy: A Medline search from 1966 to April 1998, using the terms 'asthma' and 'theophylline' and 'formoterol' or 'foradile' or 'eformoterol' or 'salmeterol' or 'long-acting beta-agonists', limited to English language, identified 23 papers. Of these, six randomised, controlled trials compared theophylline with long-acting beta-agonists.

Results:

Trial	Interventions	n	Age Range	Male %	Significant Outcomes
Pollard SJ (1997)	Salmeterol (SML) aerosol 42 μg, extended-release theophylline (THEO) capsules (individual dosage established in run-in period), or placebo, twice daily for 12 weeks.	484	12-80 years	49	SML was more effective in improving PEF, reducing the morning /evening PEF differential, and in reducing night waking. There were no significant differences in FEV_1 between SML and THEO. The SML group had greater clinical improvement, less adverse events (AEs), higher patient satisfaction with medication and used less rescue medication
Selby C (1997)	SML 50 μg bd with individually dose-titrated, sustained release, oral THEO, over 2 weeks with crossover.	15	20-66 years	47	Quality of life was higher on SML. Night waking was lower on SML. Sleep studies showed fewer microarousals on SML and fewer errors were made in the continuous attention test of visual vigilance.

Paggiaro PL (1996)	SML 50μg bd or dose-titrated, slow-release THEO capsules bd for 4 weeks.	189	17-78 years	56	Significant increase in days without rescue medication for SML compared to THEO. Incidence of GIT AEs was greater among THEO patients.
Muir JF (1992)	SML 50 μg bd or a combination of slow-release THEO 300mg and ketotifen 1mg PO, bd (TK) for 28 days with crossover.	96	17-70 years	49	SML is better than TK as regards symptom-free nights, rescue medication intake, and FEV_1. More AEs occurred in the TK group.
Fjellbirkeland L (1994)	SML 50 μg or individually dose-titrated oral THEO both twice daily over 2 weeks.	141	18-75 years	57	SML had higher morning and night PEF, less night waking, less need for rescue medication and lower symptom scores. There were more AEs in the THEO group.
Zwillich CW (1989)	Dose-titrated THEO or bitolterol (BITOL) 1.11mg TDS for 2 weeks with crossover.	26	17-47 years	58	FEV_1 was higher in THEO group. Oxyhemoglobin desaturation during sleep was less on THEO than BITOL. Subject perception of symptom control and sleep quality was better on THEO.

Comments/Limitations: Salmeterol was the only long-acting beta-agonist which has shown benefits over theophylline in a randomised controlled trial. Bitolterol (one study) was seen to be less efficacious than theophylline. Paggiaro showed decreased asthma symptoms and increased PEF using salmeterol but did not state whether these trends were significant in any way.

References:

7 Fjellbirkeland L, Gulsvik A, Palmer JBD. The efficacy and tolerability of inhaled salmeterol and individually dose-titrated, sustained-release theophylline in patients with reversible airways disease. Resp Med 1994;88:599-607.

8 Muir JF, Bertin D, French Multicentre Study Group. Salmeterol versus slow-release theophylline combined with ketotifen in nocturnal asthma: a multicentre trial. Eur Respir J 1992;5:1197-1200.

9 Paggiaro PL, Giannini D, Di Franco A, Testi R, on behalf of a European Study Group. Comparison of inhaled salmeterol and individually dose-titrated slow-release theophylline in patients with reversible airway obstruction. Eur Respir J 1996;9:1689-1695.

10 Pollard SJ, Sheldon LS, Yancey SW, Cox FM, Emmett A. Salmeterol versus theophylline in the treatment of asthma. Ann Allergy Asthma Immunol 1997;78:457-464.

11 Selby C, Engleman HM, Fitzpatrick MF, Sime PM, Mackay TW, Douglas NJ. Inhaled salmeterol or oral theophylline in nocturnal asthma. Am J Respir Crit Care Med 1997;155:104-108.

12 Zwillich CW, Neagley SR, Cicutto L, White DP, Martin RJ. Nocturnal asthma therapy: Inhaled bitolterol versus sustained-release theophylline. Am Rev Respir Dis 1989;139:470-474.

Prepared by : 1. Amanda Wilson 23 June, 1998

3 Cochrane Systematic Review:

Long-Acting Beta-Agonists Versus Theophylline For Maintenance Treatment Of Asthma

Wilson A, Gibson P, Coughlan JL.
Date of most recent substantive amendment: 12/2/1999.

Abstract

Objectives: To assess the comparative efficacy and safety of long-acting beta-agonists and theophylline in the maintenance treatment of asthma.

Search Strategy: Suitable randomised controlled trials (RCTs) were identified using the Cochrane Airways Group Database. The database was searched using the following terms: 'asthma' and 'theophylline' and 'long-acting beta-agonist' or 'formoterol' or 'foradile' or 'eformoterol' or 'salmeterol' or 'bambuterol' or 'bilolterol'. Titles and abstracts were then screened to identify potentially relevant studies. The bibliography of each RCT was searched for additional RCTs. Authors of identified RCTs were contacted for other relevant published and unpublished studies.

Selection Criteria: All included studies were RCTs involving adults and children with clinical evidence of asthma. These studies must have examined intervention with an inhaled long-acting beta-agonist: salmeterol; formoterol; eformoterol; bambuterol; bitolterol, versus ingested sustained release and/or dose adjusted theophylline.

Data Collection and Analysis: Potentially relevant trials identified by screening titles/abstracts were obtained. Two reviewers independently assessed full text versions of these trials for inclusion in the review and also assessed the methodological quality of the included trials, with particular emphasis on the allocation concealment that was ranked using the Cochrane approach. The quality scale of Jadad was also used. Where there was a disagreement between reviewers, this was resolved by consensus, or reference to a third party. Data was extracted using specially designed data extraction forms, by two independent reviewers. Inter-rater reliability was assessed by simple agreement. These comparisons were performed for each outcome. The study authors were contacted to clarify the randomisation method used, provide missing data, verify the data extracted, and identify any unpublished studies. Relevant pharmaceutical manufacturers were also contacted to obtain relevant information and unpublished studies. Outcome data was entered onto RevMan for statistical analysis. Categorical outcomes were assessed as risk reduction and 95% confidence intervals. Continuous outcomes were analysed as effect sizes with weighted or standardised mean difference as appropriate. Fixed effect models were used to obtain summary statistics for overall efficacy. Heterogeneity of results was assessed using a Chi-squared test.

Main Results: Theophylline versus a long-acting beta-agonist was reviewed in 6 RCTs of varying quality, conducted over a period of 8 years. There was a trend for salmeterol to improve FEV_1 more than theophylline (3 studies). More symptom free nights also tended to

occur with salmeterol. Biltolterol (1 study) was less efficacious than theophylline. Participants taking salmeterol experienced fewer adverse events than those using theophylline (RR 0.38;95%CI 0.25,0.57). Significant reductions were reported for central nervous system adverse events (RR 0.51;95%CI 0.30, 0.88) and gastrointestinal adverse events (RR 0.32;95%CI 0.17, 0.59).

Conclusion: Salmeterol may be more effective than theophylline in reducing asthma symptoms, including night waking and the need for rescue medication. More adverse events occurred in participants using theophylline when compared to salmeterol.

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