

REVIEW

The Cochrane Collaboration and its contribution towards the management of allergic diseases

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Introduction

Evidence-based medicine (EBM) is defined by David Sackett as 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'. In the last two decades there has been a paradigm shift in the way clinical decisions are made. This gradual shift has focused our minds more on critical examination and evaluation of the clinical evidence. As a result, nowadays less often we rely solely on content expertise, unsystematic clinical experience and intuition.

In order to be practitioners of EBM, clinicians need good evidence, which is based on robust study design, is updated regularly and is easily accessible. The Cochrane Library has as its slogan: 'The best single source of reliable evidence about the effects of health care'. So where is the Cochrane Library? and who was Cochrane? The Cochrane Library is not a place but an electronic database compiled by the Cochrane Collaboration.

The Cochrane Collaboration

The Cochrane Collaboration is named in honour of Archie Cochrane CBE (1909–88), a British medical researcher who contributed greatly to the development of epidemiology as a science. He was appointed as a Professor in Chest Medicine in 1960 at Cardiff University whilst being the director of the MRC Epidemiology Research Centre. He was best known for his influential book, *Effectiveness and Efficiency: Random Reflections on Health Services*, published in 1972 [1]. He often criticized the medical profession for not having established a system for producing up-to-date summaries of the results of reliable research about the effects of healthcare. The Cochrane Collaboration, a not-for-profit international organization, was founded in 1993 to respond to Cochrane's challenge, and evolved rapidly over the subsequent years. The Collaboration is made up of review groups, centres, fields, methods group, and the consumer network. Currently there are 14 Cochrane centres world-wide and more than 6000 people in over 60 countries work for the collaboration [2]. The Cochrane Collaboration's work is based on 10 key principles outlined in their strategic plan [3] (Table 1).

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The Cochrane Library

The Cochrane Library consists of a number of databases. These include:

- The Cochrane Database of Systematic Reviews, which contains the full text of reviews and protocols. When the need for a review is identified, the protocol for the project is written. These protocols, which are peer reviewed internally (and sometimes externally), are published in the Cochrane Library. Hence protocols are in fact reviews in the making.
- The Cochrane Controlled Trials Register.
- Database of Abstracts of Reviews of Effectiveness (DARE), which contains critical assessment and structured abstracts of other systematic reviews, conforming to explicit quality criteria.
- The Cochrane Database of Methodology Reviews, which contains systematic reviews of empirical methodological studies relevant to the synthesis of research.

When searching the library using a particular term, it automatically searches all the databases.

Systematic reviews

These reviews use explicit, rigorous methods to identify, critically appraise and synthesize relevant studies. They sometimes, but not always, use meta-analyses, which are formal, mathematical combinations of numerical results. For a systematic review to be good, it must be of high quality and appropriate. The reviews produced within the collaboration are prepared following standardized instructions and are subject to several levels of peer review. Systematic reviews control for systematic error (bias) and random error (the play of chance) in research. Recent studies have clearly highlighted that the Cochrane reviews appear to have greater methodological rigour than traditional reviews or systematic reviews published elsewhere (www.cochrane.de/cochrane/stratp96.htm and [4,5]). In addition, the collaboration continually looks at ways of improving its systematic reviews further [6]. Steps for conducting a systematic review are highlighted in Table 2.

Currently the Cochrane database of systematic reviews includes only systematic reviews of randomized controlled trials. Unlike systematic reviews published in paper-based journals, the systematic reviews within the Cochrane Collaboration are a living document, which are updated regularly. The results of systematic reviews are often summarized using a chart known as a forest plot. Forest plots show the size of the effect for each study under review as well as the combined effect of all studies. The estimate for the individual study effect is illustrated by a square whose size reflects the number of subjects in that study, together with a 95% confidence interval (CI). The combined

Table 1. The 10 principles of the Cochrane Collaboration

<i>Collaboration</i>
by internally and externally fostering good communications, open decision-making and teamwork.
<i>Building on the enthusiasm of individuals</i>
by involving and supporting people of different skills and backgrounds.
<i>Avoiding duplication</i>
by good management and co-ordination to maximize economy of effort.
<i>Minimizing bias</i>
through a variety of approaches such as scientific rigour, ensuring broad participation, and avoiding conflicts of interest.
<i>Keeping up to date</i>
by a commitment to ensure that Cochrane Reviews are maintained through identification and incorporation of new evidence.
<i>Striving for relevance</i>
by promoting the assessment of healthcare interventions using outcomes that matter to people making choices in healthcare.
<i>Promoting access</i>
by wide dissemination of the outputs of the Collaboration, taking advantage of strategic alliances, and by promoting appropriate prices, content and media to meet the needs of users world-wide.
<i>Ensuring quality</i>
by being open and responsive to criticism, applying advances in methodology, and developing systems for quality improvement.
<i>Continuity</i>
by ensuring that responsibility for reviews, editorial processes and key functions is maintained and renewed.
<i>Enabling wide participation</i>
in the work of the Collaboration by reducing barriers to contributing and by encouraging diversity.

Table 2. The main steps for conducting a systematic review

State objectives of the review and outline eligibility criteria.
Conduct a comprehensive search for studies that seem to meet eligibility criteria.
Tabulate characteristics of each study identified and assess its methodological quality.
Apply eligibility criteria and justify any exclusions.
Assemble the most complete data set possible, with the involvement of investigators if possible.
Analyse results of eligible studies, using statistical synthesis of data (meta-analysis) if appropriate and possible.
Perform sensitivity analyses, and subgroup analyses if appropriate and possible.
Prepare a structured report of the review, stating aims, describing materials and methods, and reporting results.

estimates are shown as diamonds in which the 95% CI reflects variation within and between the individual studies.

In the first issue of the Cochrane Library in 2002, there were approximately 1300 systematic reviews and over 1000 protocols (reviews in making). Achieving full coverage of all clinical areas while keeping all reviews up to date will be the Collaboration's biggest challenge.

The Cochrane Controlled Trials Register

A very useful and important feature of the Cochrane Library is the register of controlled trials, many of which are not available in other databases. In January 2002, this register had references on 327 698 controlled trials, which is over five times greater than the number of controlled trials registered in Medline since its establishment. In January 2002 searching the Cochrane Library for controlled trials in asthma, eczema and rhinitis yielded 9037, 566 and 1967 trials, respectively. The equivalent search in Medline going back to 1966 yielded 1808, 125 and 111 trials, respectively. The main reason for this difference is the number of trials, which are only published as a conference proceeding or journal supplements, which may not be indexed by electronic

databases such as Medline. In a recent study, which determined the rate at which studies reported in abstracts were subsequently published in full, it was shown that out of 573 randomized controlled trials reported as abstracts, the mean rate of subsequent full publication was 55.8% [7].

Cochrane systematic reviews relevant to allergic conditions

Cochrane systematic reviews are registered with a review group. There are currently 49 review groups covering most aspects of health care. The most prolific review group for allergic conditions is the 'Cochrane Airways Group', although the 'Cochrane Ear, Nose and Throat Disorders Group' and 'Cochrane Skin Group' also have a few systematic reviews and protocols that may be of interest to allergists. These include a systematic review on house dust mite avoidance measures for perennial rhinitis and protocols that include antihistamines and Chinese herbal medicine for atopic eczema. At present there is a total of 59 systematic reviews of randomized controlled trials relevant

to management of asthma and allergy in the Cochrane Library. Fifty-eight of these are produced by the Cochrane Airways Group. There is also a total of 56 protocols relevant to allergy, which in time will be completed as systematic reviews.

Topics covered by the 'Cochrane Airways Group' include asthma prevention (including environmental and dietary allergen avoidance and reduction measures), acute and chronic asthma and their managements (including both pharmacological and non-pharmacological treatments, side-effects of therapy, and complex interventions). The average number of trials in each review is 12 [8]. On average, the reviews include data from over 750 patients and they examine the effects of interventions on a variety of outcome measures [8]. The Cochrane Airways Group web page, with summaries of reviews, may be viewed at <http://www.cochrane-airways.ac.uk>. In the following sections three Airways Group systematic reviews, selected on the basis of their findings and relevance, are summarized in an attempt to highlight the impact of their findings on clinical practice.

Holding chambers vs. nebulisers for β -agonist treatment of acute asthma [9]

During acute exacerbation of asthma, treatment with β -agonists is often required to relieve bronchospasm. There has been some controversy on the most effective delivery methods. The objective of this review was to compare the clinical outcomes following the use of any β -agonist given by a nebuliser compared with the same β -agonist given by metered-dose inhaler with any holding chamber. The primary outcome measure was admission to hospital. The secondary outcome measures included lung function, use of steroids and length of stay in the emergency department. The review analysed 686 children and 375 adults included in 16 randomized trials from all over the world. This review revealed that amongst adult patients there

were no significant differences between the two delivery methods. The odds ratio of holding chamber vs. nebuliser for hospital admission was 1.12 (95% CI: 0.45, 2.76; Fig. 1). In children, no outcomes were significantly worse with holding chambers (odds ratio of 0.91, 95% CI: 0.4, 2.1 for hospital admission), and the available evidence suggested that in most cases holding chambers could be substituted for nebulisers to deliver β -agonists in acute asthma in the emergency department.

All Cochrane reviews identify the gaps in evidence and discuss the implications of their findings for future research. Indeed this review also clearly highlighted the much-needed research in evaluation of these devices in the community setting. In addition, as all studies excluded patients with life-threatening asthma, they highlighted the need for further studies with more severe cases of asthma.

Combined inhaled anticholinergics and β_2 -agonists for initial treatment of acute asthma in children [10]

This has been an area where in literature there were many conflicting results from a number of clinical trials. The reviewers' objectives were to estimate the therapeutic and adverse effects attributable to the addition of inhaled anticholinergics to β_2 -agonists in acute paediatric asthma. Pooling a large number of randomized trials, the reviewers reported that the addition of a single dose of anticholinergics to β_2 -agonists did not reduce hospital admission. However, significant group differences in lung function supporting the combination of anticholinergics and β_2 -agonists were observed 1 and 2 h following the dose of anticholinergic. In conclusion, this systematic review revealed that a single dose of an anticholinergic agent is not effective for the treatment of mild and moderate exacerbations and is insufficient for the treatment of severe exacerbations. In contrast, the addition of multiple doses of anticholinergics to

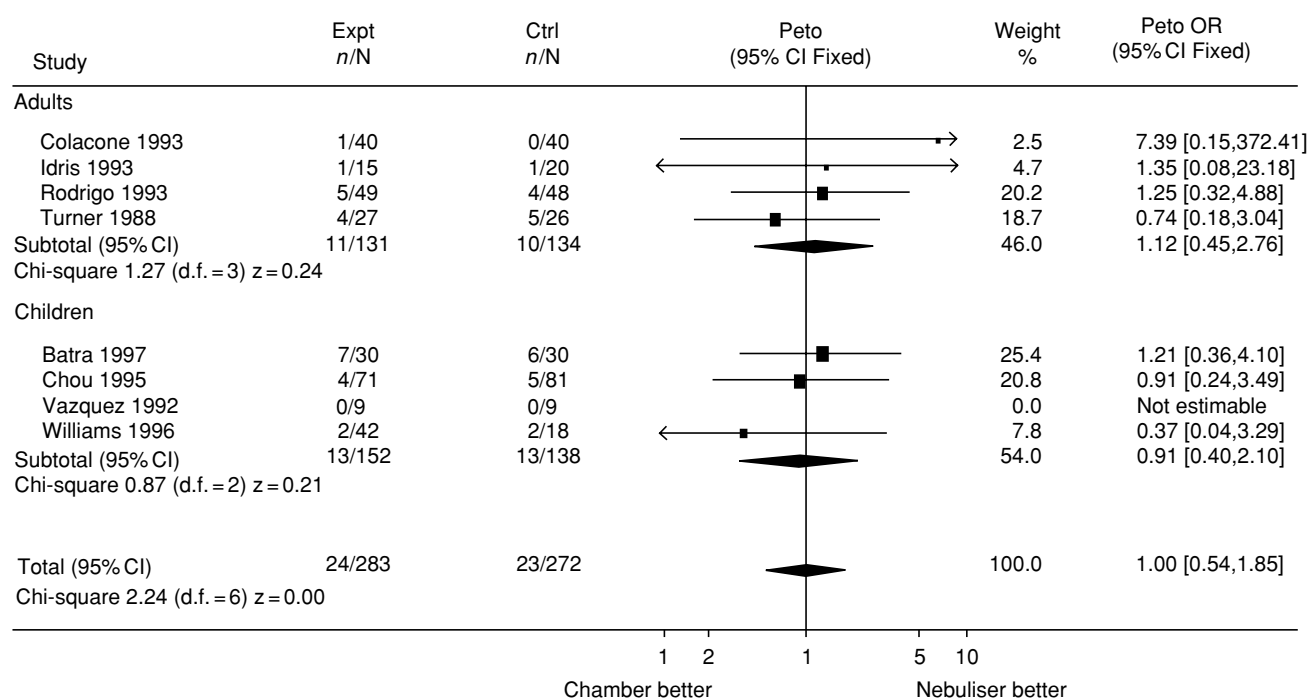


Fig. 1. Hospital admissions in adults and children using holding chambers vs. nebuliser for the delivery of β -agonists [10].

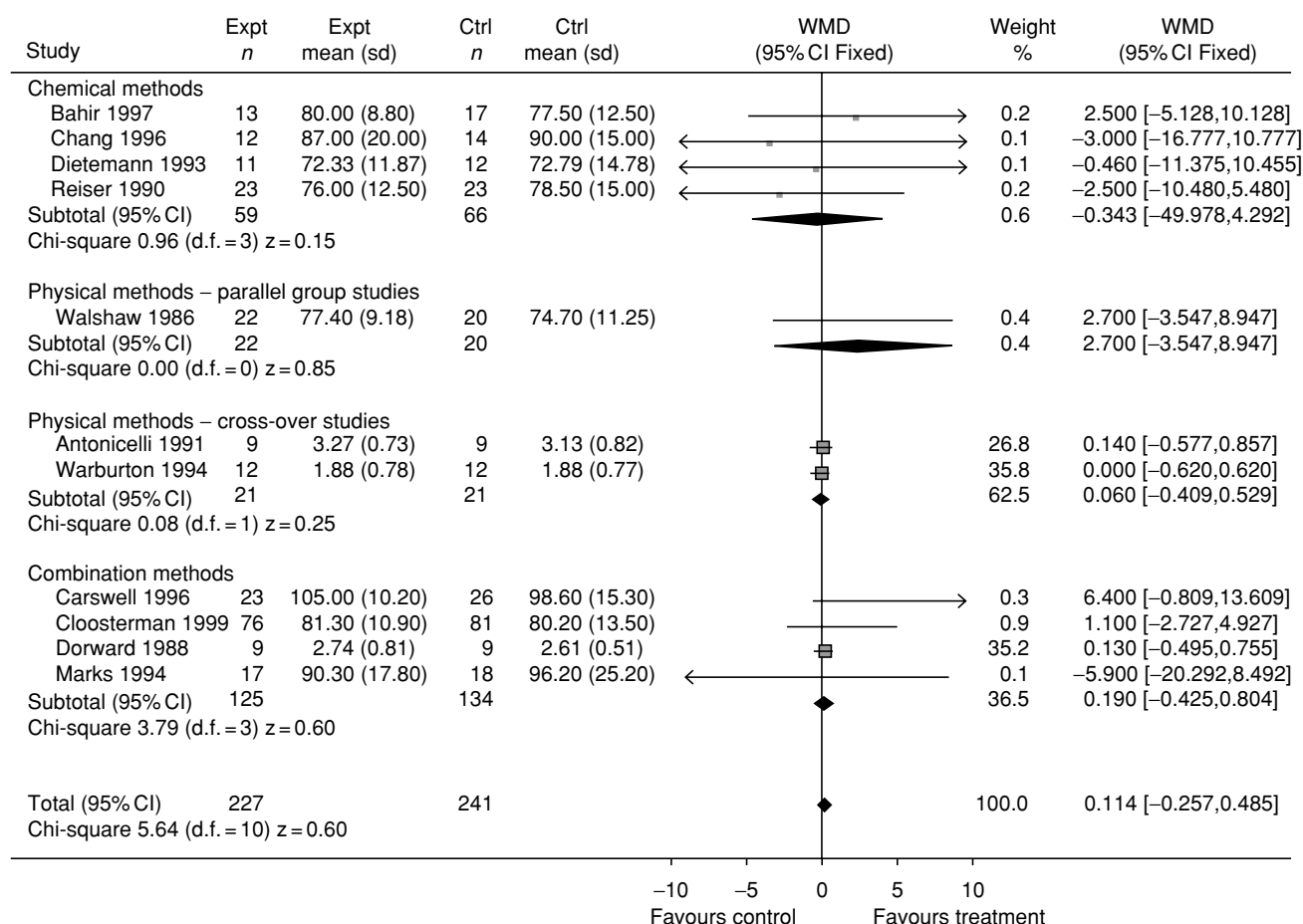


Fig. 2. Forced expiratory volume in 1 s (FEV₁) measurement reported in randomized controlled trial of house dust mite reduction measures [12].

β_2 -agonists reduced the risk of hospital admission by 25% in children with predominantly moderate and severe exacerbations. Twelve children (95% CI: 8, 32) would need to be treated to avoid one admission. For children with severe exacerbation, seven (95% CI: 5, 20) children need to be treated to avoid an admission. Interestingly, in clinical practice, many clinicians had already adopted this approach for addition of inhaled anticholinergics, but this review actually provided the much-needed high quality evidence to support this practice.

House dust mite control measures for asthma [11]

Chemical and physical methods of reducing exposure to house dust mite allergens have been investigated extensively over the last two decades. Results in the literature are contradictory and hence the objective of this review was to assess the overall effects of reducing exposure to house dust mite using chemical and physical methods separately and together. Twenty-nine trials with 939 patients were included in this review. Overall, there was no statistically significant difference in asthma improvement, asthma symptom scores, medication usage or morning peak flow (Fig. 2). The reviewers conclude that current available evidence from controlled trials of chemical and physical approaches to reduce house dust mite exposure in the homes of mite-sensitive asthmatics does not provide a sound basis for such advice. They are, however, aware that two ongoing studies, one of which is a very large trial, would provide additional

evidence that would help to clarify whether or not these strategies demonstrate beneficial effects of a worthwhile magnitude for mite-sensitive asthmatic patients.

In summary, bridging the gap between clinical research and clinical practice requires a concerted effort on behalf of researchers, clinicians, patients, managers and policy makers. The Cochrane collaboration has made striding steps towards bridging this gap.

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