

UPDATING SYSTEMATIC REVIEWS

| Klaus Linde, MD |

The Cochrane Complementary Medicine Field is the group within the Cochrane Collaboration focused on facilitating the conduct of Cochrane systematic reviews of CAM therapies. The CAM Field represents an international collaborative effort among researchers, clinicians, consumers, and CAM practitioners from nearly every continent. The Field's central office is located at the Center for Integrative Medicine, University of Maryland School of Medicine, 2200 Kernan Drive, Kernan Hospital Mansion, Baltimore, MD 21207-6697. For more information, contact Eric Manheimer at: emanheimer@compmed.umm.edu. The Complementary Medicine Field is supported by grant number R24 AT001293 from the National Center for Complementary and Alternative Medicine (NCCAM). The contents of this article are solely the responsibility of the author and do not necessarily represent the official views of the NCCAM, the National Institutes of Health, or the Cochrane Collaboration.

SYSTEMATIC REVIEWS

A major problem with systematic reviews is that they may not be up to date. If the topic is of current interest and a subject of intense clinical research, the conclusion of a metaanalysis whose literature search was completed a year previously may no longer be valid at the time of publication. In other situations, where further studies have not been performed, a 10-year-old review might still be adequate. For the general reader, it is often difficult to decide whether the review in hand truly summarizes the most current information.

The Cochrane Collaboration aims to provide healthcare professionals, consumers, and policy makers with the best available and most up-to-date evidence on the effects of healthcare interventions. Systematic reviews performed within the framework of the Cochrane Collaboration are published in The Cochrane Library, an electronic publication, which is released quarterly. One of the advantages of an electronic publication is that mistakes can easily be remedied once identified, and reviews can be replaced with an updated version if new

evidence becomes available. Cochrane reviews should be assessed and, if necessary, updated every two years or have a commentary added to explain why this is done less frequently.¹ Moher et al have proposed that a review should be considered updated if a new literature search has been performed to check whether new relevant evidence has become available, even if the search identifies no new studies.²

Although the updating of systematic reviews is extremely desirable, it is also a very difficult task. A researcher's interests often change during the career, and what was earlier a favorite topic might later be of secondary interest. Getting funds for updating is very difficult, and the rewards for publishing an update are limited. If no new trials have been done, updating is easy and limited to regular searches and statements that there is no new evidence. However, if many new trials are available, the work is considerable, and it might become necessary to do the entire review process once again. The author of this article is involved in a number of Cochrane reviews and offers the following examples to illustrate the variability and difficulties of updating.

Homeopathy for Chronic Asthma

In 1998, Kim Jobst and I published the first version of this small review. At that time, the review covered three randomized trials.³ Kim Jobst and I had a major interest in acupuncture for asthma (we had recently performed a Cochrane review on that topic⁴), and we agreed to the Cochrane Airways Collaborative Review Group's proposal to do a similar review on homeopathy to facilitate the integration of complementary therapies into the Collaboration's activities. In the following years, however, the focus of our work developed in other directions. Furthermore, this review was performed in an early phase of the Cochrane Collaboration, and it seemed necessary to redo the data extraction and assessments to meet current standards. Fortunately, Rob McCamey and Toby Lasserson took over the responsibility for updating the review. The current version covers six trials and was published in Jan-

uary 2004⁵; the review will need to be updated again soon.

Hypericum (St. John's Wort) for Depression

The first print version of our hypericum review was completed in 1996,⁶ and the first version of our Cochrane review on the topic was published in 1999.⁷ At that time, the review was already large, including a total of 27 randomized trials. In the following years, several new trials were published. Furthermore, both the characteristics and the findings of the trials showed considerable changes. The older trials had been done almost exclusively in Germany and before the use of the diagnostic criteria for major depression had become standard. Placebo-controlled trials had shown large effects over placebo, with placebo response rates generally being very low. Trials that included an active control group compared hypericum with older antidepressants such as low-dose imipramine. New trials were done in a number of countries, were mostly restricted to patients meeting the criteria for major depression, and tended to have better quality. Newer placebo-controlled trials now showed much smaller or even no effects over placebo. In comparisons with standard antidepressants, selective serotonin reuptake inhibitors were used. It is obvious that simply adding the new trials to the existing review would have been inadequate. Although the data extracted from the older trials could still be used, the concept of the review had to be reorganized, and many steps of the review process had to be redone. This took time. Another consequence of the marked changes was that the review had to be resubmitted for a full peer review. In the end, the new version of the review (now including 37 trials despite considerable narrowing of the inclusion criteria) was not available until the autumn of 2005.⁸ Since the completion of the literature search in May 2004, several additional relevant trials have been published. As the complexity of the review continues to grow, we have to think about changing the inclusion criteria once again; the new update for 2006 will require a lot of time and effort.

When we started the last update, we considered expanding the review to cover safety aspects in more detail. Case reports on serious adverse events, interactions with drugs, or systematic studies on side effects are of great interest to providers. Therefore, it would be desirable for systematic reviews to include such information. However, searching and assessing case reports and experimental studies on interactions are quite different from reviewing randomized trials. For example, information on case reports has to be obtained from drug surveillance agencies. We performed a safety review⁹ but decided not to include it in the Cochrane review. We think that we are neither able nor willing to provide the huge time resources that would be required to update this additional part of the review regularly.

Echinacea for the Common Cold

In 1999, we also published the first version of our Cochrane review of randomized or quasi-randomized trials of Echinacea preparations for the common cold.¹⁰ Most of the 16 trials available at that time dealt with combinations of Echinacea with other plant extracts. Some of the trials used alternate allocation and were not truly randomized. Since then, a number of properly randomized trials testing Echinacea mono-preparations have become available. To give the review more focus and to ensure that included trials were of adequate quality, we decided to limit the selection to properly randomized trials of mono-preparations. Thus, although the new version again includes 16 trials, it is almost entirely a new review because many of the trials included in the original review were excluded under the new criteria and new trials included.¹¹

Acupuncture for Idiopathic Headache

The currently available Cochrane version of this review was published in 2001.¹² It included 26 mostly small, randomized or quasi-randomized trials in patients with migraine, tension-type headache, both migraine and tension-type headache, or chronic headaches of undefined origin. The trials included a total of 1151 patients; some were of very questionable quality. Recently, a number of large (between 300 and more than 1000 patients) randomized trials have been performed. Some of these trials are still in the process of publication (therefore, the review has not yet been updated), but, even with the currently available trials, it is already clear that the evidence picture will

change considerably. We do not think that it will be possible simply to add the new trials to those of the old review. Instead, considerable changes in the review structure seem necessary. These will include tightening of inclusion criteria, extraction of additional outcomes, and a new metaanalytic approach. As a consequence, considerable work will be necessary to produce an adequate update.

DISCUSSION

Research on complementary therapies has made great progress in recent years. In some areas of the field, there is now considerable research activity, and new evidence is becoming available rapidly. New trials often have better quality and larger sample sizes than older studies. The number of persons with both methodological skills and practical expertise in complementary therapy is increasing. These positive developments have important consequences for systematic reviews.

In the past, many systematic reviews were performed by individuals or groups with mainly methodological skills. Such groups often work on broad and changing topics (for example, a variety of complementary therapies without a limitation to defined conditions) depending on current interest or availability of grants and produce a considerable number of systematic reviews. It is obvious that this is not a good basis for regular updating. It would be desirable that the responsibility for Cochrane reviews goes more and more to individuals or groups with a clear clinical and scientific focus on the intervention and the condition of interest.

In this author's opinion, the long-term success of the Cochrane Library and the Cochrane Collaboration will be dependent largely on successful updating. Taking responsibility for a highly respected review can be an attractive proposition, particularly if the review reflects the researcher's "core" area of interest. However, additional reward mechanisms must be developed to encourage regular updating. Also, without adequate funding mechanisms, it will be impossible to make regular updating routine.

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