EXPLORING, EVALUATING, AND APPLYING THE RESULTS OF SYSTEMATIC REVIEWS OF CAM THERAPIES

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Providers of complementary and alternative medical treatments are often very busy with their clients, leaving them little time to keep up to date with research developments in their field. However, a failure to keep current with research findings can have serious adverse consequences for patient care, including the continued recommendation and use of therapies proven ineffective or even harmful by randomized controlled trials, as well as a delay in the uptake of treatments proven to be effective.[1] Systematic reviews provide an efficient and timely way for complementary and alternative medicine (CAM) providers to keep abreast of new research.[2] Systematic reviews use explicit and well-documented methods to review existing research on the effectiveness of medical treatments, as evaluated by randomized controlled trials (RCTs).

The Cochrane Collaboration is an international, nonprofit, and independent organization dedicated to making up-to-date, accurate systematic reviews of the effects of healthcare available worldwide.[3] The 10,000 individuals who compose the Cochrane Collaboration[4] include researchers, clinicians, volunteers, and librarians, all driven by enthusiasm and a desire to learn the truth about the value of different healthcare therapies. Most do not receive payment for any work they do within the Collaboration.[5] The Cochrane Collaboration's principle product, *The Cochrane Library*, consists of a regularly updated collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews, which, as of January 2005, included 2,249 Cochrane Reviews, of which over 150 relate to complementary and alternative therapies.

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INTRODUCING *THE COCHRANE COLUMN* IN *EXPLORE*

To support the dissemination of Cochrane Reviews in CAM, *EXPLORE* has partnered with the Cochrane CAM Field at the University of Maryland Center for Integrative Medicine to launch the publication of a new series called *The Cochrane Column*. Each column in the series will begin with a brief clinical scenario in which a clinician considers the possible value of a CAM therapy for treating a client presenting with a health condition. The column then includes the reproduction of a relevant Cochrane Review abstract, followed by an overall critical appraisal of the Cochrane Review. *The Cochrane Column* concludes with an evidence-based answer to the question raised in the clinical scenario. As an introduction to *The Cochrane Column*, we have provided below (1) an overview of the unique attributes of Cochrane Reviews, (2) an introduction to some of the issues surrounding the critical appraisal of Cochrane Reviews, and (3) a brief discussion of the relevance of Cochrane Reviews to clinicians and researchers.

PART I. COCHRANE REVIEWS: EXTENSIVELY PEER REVIEWED, REGULARLY UPDATED, AND INDEPENDENTLY PRODUCED

Cochrane Reviews are often considered the gold standard of systematic reviews because they undergo a strict and meticulous peer-review process, are regularly updated, and are largely free from commercial conflicts of interest. Each Cochrane Review is peer-reviewed twice—first at the research plan or *protocol* stage and later when the review has been completed. The international network of peer-reviewers and editors, based in some of the most renowned research institutions in the world, evaluate the review on methodology and study design, statistics, and content area issues. An extensive network of CAM content area experts, including specialists in acupuncture, herbal medicine, and massage, ensure that the review assesses the validity of the CAM treatments administered in the trials. CAM experts might evaluate whether the acupuncture treatment administered was adequate or whether the Chinese herbs used were appropriate for the problem treated. Assessing validity of the treatment procedure is important because, for instance, basing conclusions about acupuncture efficacy on a suboptimal procedure is "analogous to a pharmaceutical trial formulating conclusions about the efficacy of a drug based on an inadequate dose."[6] Consumers, who represent the viewpoint of patients and the lay public, are also often involved, reviewing the review for language and accessibility. For instance, the language in a Cochrane Review title was recently changed from *gravidae striae* to *stretch marks* after a CAM consumer pointed out that *stretch marks* is a more recognizable term to the general public.

The peer review of Cochrane Reviews continues even after their publication. Any reader finding problems or gaps can comment using the "Comments/Criticism" button at the top of each review. These comments are posted on the Internet and compiled and published, together with the review, on the next release of *The Cochrane Library*. Reviewers work with criticism editors to respond to these comments and to take these comments into consideration when updating their review. Updates of reviews take into account any eligible new trials as well. Because the

RCT evidence base on CAM topics can change so rapidly, the regular updating of Cochrane Reviews, made possible through the electronic publication of *The Cochrane Library*, is critical for ensuring that *The Cochrane Library* remains an up-to-date and accurate source of the effects of CAM therapies. The Cochrane Review *Acupuncture and dry-needling for low back pain*[7] shows how a few years can result in changes of a review's conclusions and, consequently, illustrates the importance of updating reviews. This review was first published in April 1999, and, at that time, the reviewers concluded that, "the evidence does not indicate that acupuncture is effective for the treatment of back pain." Over the next 5 years, several additional high-quality trials with positive results were published and incorporated into the review, and, by January 2005, the review concluded that "there appears to be some evidence that meridian acupuncture is better than no treatment or sham treatment for chronic low back pain."[7] In contrast to Cochrane Reviews, which are adaptable, reviews published in print journals are fixed and are therefore obsolete shortly after publication.

Another distinguishing feature of Cochrane Reviews is that they are largely free from the financial conflicts of interest that have the potential to distort and exaggerate findings. To ensure that Cochrane Reviews are not biased by funding from industry groups that stand to gain financially from a review's results, the Cochrane Collaboration has instituted a policy that prohibits any commercial entity from funding either an individual Cochrane Review or the Cochrane Collaborative Review Group administrative infrastructure that produces the reviews.[5] One recent example that might be interpreted as bias resulting from industry financing is the conflicting results of systematic reviews on the cardiovascular risks of the withdrawn painkiller Vioxx (Merck Research Laboratories, Whitehouse Station, NJ): Two industry-financed systematic reviews suggested that there was no excess cardiovascular risks of Vioxx, as compared with NSAIDS and placebo,[8,9] whereas a nonindustry funded systematic review,[10] published in the prestigious medical journal *The Lancet*, indicated that Vioxx was associated with a greater than two-fold increased risk of cardiovascular events, compared with other NSAIDS or a placebo. Excess cardiovascular risks of Vioxx were the reason given for the drug's eventual withdrawal from the marketplace.[11–13]

PART II. CRITICALLY APPRAISING COCHRANE REVIEWS: INVESTIGATING SOURCES OF BIAS

Evaluating reviews for potential bias will be a primary objective of *The Cochrane Column*. In the context of systematic reviews, the term *bias* is used to designate some systematic study-related error that causes the treatment-outcome association *in the systematic review* to not reflect the true association between the treatment and the outcome *in the real world*. Future columns will serve to illustrate the two primary sources of bias in systematic reviews: (1) bias from the individual studies included in the review and (2) bias in the way the review is carried out.

Cochrane Reviews and Randomized Controlled Trials

For Cochrane Reviews, the individual studies included are generally restricted to RCTs, widely regarded as the most unbiased study design for evaluating healthcare interventions. In an RCT, participants are randomly allocated to two or more comparable groups. Next, an intervention is administered: one group is given a real therapy (eg, acupuncture or herbs), and the other group is given a "control" (eg, sham acupuncture or sugar pills). After some time, an outcome is recorded. If the group receiving the real therapy fares better than the group receiving the control, then the benefits should be attributable to the real therapy because the groups were initially comparable, right after the random allocation and before the intervention was administered.

The Cochrane Collaboration has invested substantial resources toward the identification of RCTs by conducting extensive electronic searches of the major bibliographic healthcare databases, as well as page-by-page "handsearches" of the world's healthcare research literature. This intensive international effort has resulted in the construction of the Cochrane Central Register of Controlled Trials,[14] the most comprehensive database of controlled trials in the world and the primary data source for Cochrane Reviews. Many of these trials are CAM-related.[15] Because of the extensive centralized efforts invested in identifying and compiling RCTs, individual Cochrane reviewers today are much more likely than they were 10 years ago to locate a complete and representative set of eligible RCTs.

However, problems in locating all the relevant RCTs persist, and RCTs, although preferable to observational studies, are not uniformly free of bias, and they must be critically evaluated. The initial steps in carrying out a systematic review therefore consists of a thorough search of multiple sources to locate relevant RCTs, followed by an evaluation of RCTs for eligibility, and then a critical evaluation of the RCTs included. The final steps include calculating the results from the RCTs (and combining them if appropriate) and interpreting the results.[16] Each of these component steps is briefly introduced below, and will be further illustrated in future columns, in reference to specific CAM-related Cochrane Reviews.

Steps in Carrying Out a Systematic Review

Locating studies. Identifying relevant trials has been described as "the most fundamental challenge" in preparing a systematic review.[17] Searching for trials using a sensitive and efficient approach can be challenging and time-consuming, yet it is also fundamentally important. After all, conducting well-designed searches, documented with sufficient detail so that they can be reproduced, is largely what distinguishes a systematic review from a traditional narrative review.

A thorough search is especially important in CAM in which the trials that exist may not be found by searching only the standard sources. For example, in the highly influential systematic review of St. John's wort for depression,[18] it was found that "searches in Medline, Embase, Psychlit, and Psychindex revealed less than one third of the trials." Future installments of *The Cochrane Column* will evaluate the adequacy of searches and also evaluate whether the reviewers considered the effects of any limitations of their searches in the interpretation of their results.

Determining eligibility. In Cochrane Reviews, a protocol is required that must specify which studies will be eligible. Eli-

gibility is expressed on the following four components: healthcare condition (eg, low back pain), outcomes examined (eg, pain, functional status, and analgesic use), therapies compared (eg, needle acupuncture vs sham acupuncture, no treatment, or any other active therapy), and eligible study designs (eg, RCTs only). These eligibility criteria, prespecified in the Cochrane Protocol, should later be adhered to when reviewers make decisions about whether identified studies can be included in the Cochrane Review. Requiring prespecification of these eligibility criteria in the Cochrane Protocol guards against reviewers later selectively picking and choosing only those studies that best match their point of view or best serve their interests. Prespecification of outcomes that will be abstracted from eligible studies is also required in a Cochrane Protocol, for similar reasons.[19]

Assessing validity. Although RCTs, in general, are the best study design for evaluating therapies, all RCTs are not of uniform quality. A substantial body of research has now demonstrated that specific quality defects in an RCT can result in spuriously exaggerated treatment effects.[20–22] Therefore, quality evaluation of included RCTs is another critical component in the preparation of Cochrane Reviews. Some key criteria on which RCTs are evaluated include the quality of the method of randomization, the blinding of patients and/or evaluators to the treatment received, and the accounting for study participants who dropped out. There are various methods for incorporating quality assessments in a systematic review, including assigning greater weight to higher quality trials or only including the higher quality trials in a subgroup analysis. Some of these methods, as well as their limitations, will be reviewed in future columns. Future columns will also explain each of the key quality criteria in more detail and will discuss the special challenge that the double-blinding criteria poses for investigators conducting trials of "hands-on" CAM therapies such as massage, acupuncture, and chiropractic.

Combining the studies. It is useful to examine whether or not the trials included in a review are sufficiently similar in design that it makes sense to combine them. The Cochrane Review *Acupuncture for smoking cessation*,[23] for example, included within its scope RCTs evaluating any form of acupuncture (eg, needle acupuncture, acupressure, laser acupuncture, electrostimulation) as compared with any type of control (eg, sham acupuncture, no treatment, advice). Because the reviewers judged, appropriately, that different variants of the acupuncture procedure, as well as the use of different controls, might result in different treatment effects, they performed separate analysis, stratified by type of acupuncture studied and type of control used. Using this clear approach to the analysis, and avoiding the "combining of apples and oranges," the reviewers concluded that "there is not clear evidence that acupuncture, acupressure, laser therapy, or electro-stimulation are effective for smoking cessation."

Future columns will discuss issues related to clinical and methodological diversity, as well as statistical heterogeneity, which must be considered in deciding whether or not to conduct a quantitative synthesis of the data from the different trials or a *meta-analysis*. Appropriate uses of the different statistical methods of combining data and expressing the combined results graphically and numerically will also be examined.

Interpreting the results. Reviewers should exercise prudence in interpreting the RCT data and should not overstate the benefits of a therapy nor make any conclusions that cannot be supported with the data. Such thoughtful interpretations of the data should take into account not only statistical significance but, also, crucially, the number, quality, consistency, and sizes of the studies reviewed.

In the Cochrane Review *Acupuncture for smoking cessation*,[23] for example, only one RCT of acupressure was identified, and, according to this small RCT, acupressure was significantly better than advice. However, the report of this single RCT was unsatisfactory, lacking detail and containing a numerical error. Therefore, the reviewers appropriately concluded that for acupressure (as well as for all other forms of acupuncture-type therapies), there is no clear evidence of effectiveness for smoking cessation. Future installments of *The Cochrane Column* will evaluate the success of reviewers in adhering to an evenhanded, impartial, and supportable interpretation of the data.

PART III. CLINICAL RELEVANCE AND COCHRANE REVIEWS

In determining whether a review's results are applicable to a patient's care, it is important to consider the similarities and differences between the patients and interventions evaluated in the review and the clinical situation at hand. Each Cochrane Review includes an *Implications for Practice* section that spells out the specific patients and particular interventions to which the review's results could reasonably be applied. In the Cochrane Review *St. John's wort for depression*,[18] for example, the *Implications for Practice* section suggests that the short-term use of hypericum "might be valuable [for patients with] less severe forms of depressive disorders." In terms of the potential use of variations of the St. John's wort preparations studied in the trials, the reviewers note that "The preparations tested in the summarized randomized controlled trials are all extracts prepared according to the German monograph for this herb. Physicians who want to prescribe hypericum should be aware that preparations might differ considerably in their content of potentially active ingredients."

In evaluating clinical relevance, it should also be assessed whether the benefit associated with a therapy, as estimated by the results of the review, would have a meaningful impact on a patient's condition and whether or not benefits would be outweighed by adverse effects, inconvenience, or associated costs. Considering that St. John's wort is convenient and easy to use, and also associated with fewer adverse effects[18] and lower costs[24] than some standard antidepressants, the reviewers suggest that a clinician might consider a validated St. John's wort preparation as a viable treatment option for a patient with a less severe form of depression who is not taking other medications with which St. John's wort may interact.[25]

A clinician would also want to occasionally refer back to *The Cochrane Library* to be sure that the evidence supporting a therapy's use has not changed or been overturned. For example, some recently

published, large RCTs have failed to show strong efficacy of St. John's wort. The inclusion of these RCTs in the next update of the Cochrane Review of St. John's wort may result in a depreciation of the Review's estimates of the herb's benefits.

PART IV. COCHRANE REVIEWS: IMPLICATIONS FOR RESEARCH

Cochrane Reviews are as highly relevant to researchers as they are to practitioners, and, in fact, each Cochrane Review concludes with a section called *Implications for Research*, in which the reviewers specify any research questions that remain to be addressed, and any RCTs that remain to be conducted, to fill in existing gaps in the knowledge base. The Cochrane Review *Acupuncture for smoking cessation*,[23] for example, found that, in most cases, the RCTs suggest little or no benefit and that, therefore, future RCTs of acupuncture for smoking cessation should not be a top priority. However, of the 22 RCTs included in this review, two did show a benefit of acupuncture as compared with sham acupuncture. In both of these trials, acupuncture was administered with an adequate stimulation and was followed by sustained ear acupressure. Therefore, in the *Implications for Research* section of this review, the authors suggest that any future trials of acupuncture for smoking cessation should use the same acupuncture protocol as that administered in these two positive trials to confirm or refute the preliminary suggestion of a benefit.

Clinical trial researchers are increasingly being expected to plan their studies against the backdrop of the existing knowledge, as summarized in systematic reviews. For example, research-funding agencies, including the UK Medical Research Council, now require evidence of a systematic review before they consider whether to fund a new RCT.[26] The systematic review serves to ensure that the proposed trial is relevant and necessary and also helps to assure that investigators designing the new trial bear in mind the challenges encountered and lessons learned from the earlier trials. With the vast number of research questions that still remain to be addressed in CAM, and with the limited financial support available to study nonproprietary CAM therapies, it seems worthwhile to promote a greater awareness, especially among CAM researchers, of the importance of planning a study in the context of what is already known on a topic.

CONCLUSION

In this era of evidence-based medicine, high-quality data from RCTs and systematic reviews trump expert opinion, pathophysiological rationale, clinical observation, or tradition. Limited healthcare resources will increasingly be allocated only to those therapies that are backed up by systematic reviews of well-designed RCTs. Evidence-based medicine proponents would argue that this system allows for the most equitable distribution of the limited and dwindling resources that governments, as well as other funders, have available to spend on healthcare.[27] To justify the support for CAM therapies among funders of health services, it will become more and more important to maintain and disseminate a well-developed database on the evidence of the effectiveness of CAM treatments.

The development of the knowledge base of the effects of CAM therapies is already well underway. For example, only 20 years ago, RCTs in CAM were scarce, and methods for systematically reviewing RCTs of healthcare therapies had not yet been developed. Since then, significant progress has been made in the number and quality of RCTs conducted in CAM, the advancement of systematic review methods for evaluating such trials, and the development of the international Cochrane Collaboration to support such meticulous evaluation. The creation of this evidence is only the first step toward changing practice, however.[28] The evidence must also be disseminated widely and put into practice before it can have a positive impact on clinical care and policy decisions. Initiatives aiming to equip CAM clinicians and researchers with the core skills and competencies to critically appraise the scientific studies and apply the results of this assessment to patient care are already underway in other CAM journals.[29–31] With the launch of *The Cochrane Column*, *EXPLORE* joins these earlier endeavors but concentrates specifically on the dissemination and critical review of the systematic reviews created over the past 12 years by the thousands of dedicated researchers around the world who comprise the Cochrane Collaboration. Only by widely disseminating Cochrane Reviews and other high-quality research studies among clinicians, patients, and policy makers will it be possible to make evidence-based CAM a reality.

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