The Ninth Cochrane Dermatology Meeting, British Association of Dermatologists, London - Advances in Conducting Systematic Reviews

Dr. Antonio AT Chuh

MD(HK) FRCP(irel) FHKCP FHKAM(Family Medicine)

Part-time Associate Professor, Department of Community and Family Medicine, The Chinese University of Hong Kong
Honorary Clinical Assistant Professor, Family Medicine Unit, Department of Medicine, University of Hong Kong

Introduction

The Ninth Cochrane Dermatology Meeting was held on 10-11 September 2004 at the Headquarters of the British Association of Dermatologists. This annual conference is held in venues within and outside the United Kingdom in alternate years. Dermatologists, family physicians, epidemiologists, statisticians, and other investigators presented their original research and contributions to dermatology reviews.

The Cochrane Skin Group

Professor Hywel Williams, Consultant Dermatologist and Professor of Dermato-Epidemiology, Queen’s Medical Centre, University of Nottingham extended a warm welcome to invited speakers and international delegates. He emphasised that the purpose of the meeting is not to discuss treatments of individual dermatological diseases in great details, but to explore agenda and advances in conducting systematic reviews and managing cutaneous diseases in an evidence-based manner.

Photodynamic therapy for squamous cell carcinoma and its precursors - the value of searching beyond literature in the English language

Dr Maggie Westby, United Kingdom Cochrane Centre, Oxford, presented results of her ongoing review on photodynamic therapy for squamous cell carcinoma. She pointed out that at least six months follow-up should be regarded as adequate when judging responses to photodynamic therapy. However, most published studies adopted only two to four months evaluation of long-term effects on relapse and adverse reactions follow-up to document the outcome measures, rendering least six months follow-up should be regarded as adequate difficult.

As clinical diagnosis without histopathological confirmation is acceptable in many circumstances, the general consensus of the forum is that histopathological confirmation is unnecessary for studies on precursors of squamous cell carcinoma.

Photodynamic therapy on precursors of squamous cell carcinoma, namely actinic keratosis and Bowen’s disease. A major difficulty is whether histological diagnosis should be mandatory for clinical trials involving these cutaneous diseases. As clinical diagnosis without histopathological confirmation is acceptable in many circumstances, the general consensus of the forum is that histopathological confirmation is unnecessary for studies on precursors of squamous cell carcinoma.

Dr Westby also highlighted the importance of handsearching in addition to Medline search in locating randomised controlled trials. It is more likely for studies with statistically and clinically significant results to be accepted by indexed journals than for studies reporting statistically insignificant results or statistically significant but clinically insignificant results. Searching on Medline alone thus renders a review prone to publication bias.

The forum responded that for similar reasons, searches for clinical trials should explicitly include reports published in languages other than English. The difficulties in obtaining full text of such reports and the expenses incurred in translating such into English are not excuses for omitting high quality trials in other languages.

Evening primrose oil for atopic dermatitis - implications in reviewing trials in alternative and complementary medicine

Dr Katja Schmidt, Peninsula Medical School, University of Exeter, presented her review on evening primrose oil and borage oil for the management of atopic dermatitis. Dr Schmidt reported her difficulties of searching for credible clinical trials in alternative therapies. However, as complementary and alternative therapies are widely accepted by medical practitioners and the public, high quality systematic reviews are eminently necessary. Professor Williams also shared the political and legal implications of academic activities in these areas.

Minocycline for acne vulgaris - the value of searching beyond Medline

Dr Sarah Garner, St George’s Hospital Medical School, University of London, reported her updated review on the use of minocycline for acne vulgaris. Dr Garner’s experience was that while previous reviews included only one to three randomised controlled trials, she and her co-investigators searched Medline, EMBASE, Biosis, Biological Abstracts, International Pharmaceutical Abstracts, Cochrane Skin Group’s Trial Register, Theses Online, BIDS ISI Science Citation Index, National Research Register, Current Controlled Trials and BIDS Index to Scientific and Technical Proceedings. They also searched for the references of articles retrieved, and communicated with international investigators and pharmaceutical companies. In the end, they included as many as 27 randomised controlled trials. Dr Sarah emphasised the importance of including ongoing clinical studies despite the intrinsic difficulties incurred thereof.

The forum in general concurred that systematic reviews performed under the auspice of Cochrane are likely to be more impartial, comprehensive, and evidence-based than reviews by authoritative investigators who themselves might be involved in some of the clinical trials. On a consonant note, members of the forum reminded that it is now a policy of Cochrane for clinical trials to be pre-registered with professional bodies before launching.

Pityriasis rosea - novel DNA sequence-based virological findings have led to irrational treatments
Dr Antonio Chuh, family physician in Hong Kong and leader of the Cochrane review group in pityriasis rosea,2 presented some of his studies3-10 and a review11 in pityriasis rosea. He emphasised that pityriasis rosea is a common dermatological condition and can exert significant impacts on the quality of life of patients.12 Recent DNA sequence-based virological findings and controversies in its aetiology13-14 have led to antibiotics15 and antiviral agents16 being advocated for its management, despite the rash being self-limiting and despite the efficacy of such treatments being in doubt.17 The injudicious use of antibiotics and antivirals might lead to hypersensitivity and adverse reactions for the patients, and risks of development of microbial resistance which might affect the community as a whole. The costs incurred in adopting therapies not yet proven to be effective are difficult to be justified.

Dr Chuh posed the dilemma of including quasi-randomised trials such as randomisation by alternative allocation18 in systematic reviews to the forum. The general consensus is that such trials should not be included in the body of the review, but might be discussed as a side issue. Dr Chuh also shared his difficulties in recruiting a consumer reviewer in his group, and that the involvement of lay persons in academic publications is a relatively alien concept for the local Chinese population in Hong Kong.

Dr Tina Leonard, Centre of Evidence-based Dermatology, University of Nottingham, responded that the role of consumer reviewers is to ensure that patient-centred outcome measures such as effects on quality of life are included in the review. She stressed that a tradition of the Cochrane Skin Group is to adopt impacts on quality of life as primary rather than secondary outcomes. Another role of consumer reviewers is to ensure that the final report is written in a style understandable to patients, administrators, and healthcare workers alike.

To evidence and beyond - applying evidence back to the bedside

Professor Williams lectured on how to apply the evidence back to the bedside.19 He stated that the four steps of evidence-based medicine are to ask an answerable structured question, to perform an appropriate search, to critically appraise the evidence, and then to apply the evidence back to patients. The two issues to consider in such application are internal validity, i.e. how true the results are, and external validity, i.e. whether the results can be applied to individual patients. Patients may differ in biological manners, disease subtypes, social factors, presence or absence of comorbidities, and baseline risks of benefits and adverse effects.

Professor Williams also discussed the differences between mean response and spread of response. Two treatments may have the same mean response in that both are significantly more beneficial than placebo. However, one may have a narrow spread of response, i.e. most patients experiencing at least some benefit, while the other might incur a wide spread of response, i.e. some patients benefitting from marked improvements while some having little or no improvement. If possible, both mean response and spread of response should be analysed in systematic reviews.

Values and limitations of subgroup analysis

Dr Jo Leonardi Bee, Statistical Editor of the Cochrane Skin Group, presented the advantages and limitations of subgroup analysis. She first demonstrated the differences between statistical heterogeneity and clinical heterogeneity. While confronting little or no heterogeneity for the entire patient population, reviewers might separate the patients to search for statistical heterogeneity within smaller patient populations. Notable examples are subgroup analysis for topical and systemic treatments, e.g. topical and systemic PUVA, low dose and high dose therapies, short-term and long-term adverse reactions, and disease subgroups, e.g. chronic plaque psoriasis and palmoplantar psoriasis.

However, Dr Bee warned that overdoing subgroup analysis invites false positive results owing to randomisation effects. If a p value of less than 0.05 is taken to be the cut-off point for statistical heterogeneity, a reviewer can reasonably predict one positive result by doing 20 subgroup analyses. Such positive results would be misleading and not be indicating clinical heterogeneity. Subgroup analysis should therefore be performed only if sub-populations in the patient pools have inherent, disease- or treatment-related, and biologically plausible differences. It is also desirable to indicate the intention to perform subgroup analysis in the protocol, rather than performing such after the protocol is approved and no significant results are found on collective analysis of trial results.

Treatments for melasma - adverse effects should be searched for beyond randomised controlled trials

Dr Luis Gabrielle Cuervo, a consultant dermatologist from Columbia, discussed his difficulties in doing a systematic review on treatments for melasma. A specific issue is that adverse reactions of treatments are rarely reported in randomised controlled trials. The most severe spectrum of adverse effects is usually reported as isolated case reports, sometimes in local non-indexed journals. Case reports from various indexed and non-indexed sources should therefore be actively searched for, in addition to the electronic databases for adverse drug reactions.

Hand dermatitis - the pertinence of using standard treatment modalities as controls

Professor Pieter-Jan Coenraads, Dermatology Department, Groningen University Hospital, the Netherlands, shared his long interest in hand dermatitis.20, 21 He reported his analysis results for treatments in hand dermatitis. Professor Coenraads hand-searched and retrieved 29 randomised controlled trials.22 However, he commented that the results were difficult to interpret. Firstly, variants of hand dermatitis were not described in many studies, not to speak of secondary causes such as metal allergies which might not have been excluded before recruitment. Secondly, the methods of randomisation concealment were not disclosed in many studies. Thirdly, bilateral comparison (right hand against left hand) studies are difficult to be analysed.

The most pertinent deficiency Professor Coenraads remarked on the published studies is that standard treatments were not used as controls. Most dermatologists would opine that topical corticosteroids are the standard treatment for hand dermatitis after excluding secondary causes. Many published studies adopted placebo, ultraviolet phototherapy, and even obsolete radiation therapy as controls, rendering cross-comparison between studies difficult.

Roles of lay consumers in systematic reviews

Dr Avanta Collier from the Department of Dermatology, Health Science Center, University of Colorado, presented her findings in a survey on consumer reviewers in Cochrane. Most consumer reviewers have chronic diseases and are happy to be involved in the projects. They find themselves useful as part of the team but...
may be intimidated when professional jargons are interchanged instead of lay terminologies. Cochrane arranges training for consumer reviewers and most find such training useful.

Four consumer reviewers presented their views on their roles in the Cochrane projects. All have chronic dermatological ailments. They reported high valuation of their involvements by the medical members of the group. They received adequate training to enhance participation in the earliest steps in a review, i.e. justifying the necessity of the review and registering the project with Cochrane, and the final steps of the review, i.e. ensuring that the final report is reader-friendly to the lay public.

Some consumer reviewers are professionals or scientists in fields other than medicine in their own right. They actively participate in other processes, such as drafting protocols, searching and retrieving data, performing meta-analysis and subgroup analyses, and be peer reviewers for protocols and reports.

Messages to medical practitioners in Hong Kong

None of us can afford the time to critically appraise original research articles in all aspects of our professional practice. Systematic reviews assist in our practice of evidence-based medicine. Such has to be produced in logical steps with smooth internal communication and valid external scrutiny.

The Cochrane Collaboration is one of the organisations providing guidance and assistance in the production of systematic reviews. Other professional organisations in evidence-based health informatics include the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/), the Oxford Centre for Evidence-Based Medicine (www.cebm.net/), the Centre for Reviews and Dissemination, University of York (www.york.ac.uk/inst/crd/), and the Health Information Research Unit, McMaster University (hiru.mcmaster.ca/).

Whilst articles in indexed international journals have to undergo one peer review process, Cochrane reviews have gone through at least two peer review cycles: both the protocol and the final report are peer reviewed. Most reviews include not only indexed journals but also local journals, conference proceedings, trials conducted by pharmaceutical companies, unpublished studies where available, and data from ongoing studies where possible. Trials reported in languages other than English are included if technically feasible.

Consumers are encouraged to take part in all processes of the review. For some areas such as skin diseases, protocols and reviews without the active involvement of consumer reviewers are highly unlikely to be accepted. Published reviews are regularly updated by the original group, or by another group should the original group fail to achieve such on time. The final products are high quality reviews based on the best currently available evidence, with minimal publication bias, and in a writing style comprehensible to professionals and the public.

Abstracts of published Cochrane reviews may be accessed via Medline or at the Cochrane Library (www.update-software.com/cochrane/abstract.htm). Practitioners with a dedication in contributing to Cochrane reviews may contact the Cochrane Collaboration (www.cochrane.org/), the Chinese Cochrane Centre (www.chinacochrane.org/), the Hong Kong Branch of the Chinese Cochrane Centre (www.hkcochrane.cuhk.edu.hk/), or the United Kingdom Cochrane Centre (www.cochrane.org/).

The ultimate aims of systematic reviews are to promote and facilitate the practice of evidence-based medicine. Reviews are distinct from guidelines. It is up to the clinician to decide how best to use the evidence for the benefit of his patient, sometimes with the decision making shared between the clinician and the patient. Clinical independence of the doctor and individuality of the patient are not hampered in the process. The value of the consultation process is treasured as it always should be. The truth may never be known to us, although the facts are. Basing the decision making on the best evidence is likely to be nearer to the truth. As stipulated in the logo of the Cochrane Skin Group: the truth is out there.

References: