ORAL DISEASES

Oral Diseases (2010) 16, 592–596. doi:10.1111/j.1601-0825.2010.01674.x

www.wiley.com

INVITED MEDICAL REVIEW

Using Cochrane reviews for oral diseases

HV Worthington[1], A-M Glenny[1], L Fernandez Mauleffinch[1], F Daly[2], J Clarkson[2]

[1]*Cochrane Oral Health Group, School of Dentistry, The University of Manchester, UK;* [2]*Dental Health Services & Research Unit, University of Dundee, UK*

OBJECTIVES: To provide readers with information about the Cochrane Oral Health Group and how the reviews on oral diseases have contributed to guideline developments and the commissioning of trials.

MATERIALS AND METHODS: Examples have been selected from the reviews published on The Cochrane Library. Descriptions are given of how these reviews have been used in guideline development and commissioning of trials. Readers are updated on reviews focused on the management of oral cancer and the new venture of diagnostic test reviews.

RESULTS: Reviews on the management of oral diseases due to cancer treatments have been included in guidelines and changed practice in the UK. Cochrane reviews on Bell's Palsy have led to a randomised controlled trial which has changed the evidence base. The Cochrane review on recall intervals between routine appointments has input into the NICE guideline and resulted in a randomised controlled trial to look at different intervals including a risk-based interval.

CONCLUSION: We hope this article will give readers information on the work of the Cochrane Oral Health Group and insight into the diversity of reviews in oral diseases. The reviews are successfully being used to change practice and as background for the funding of large-scale clinical trials.

Oral Diseases (2010) **16**, 592–596

Keywords: Cochrane Oral Health Group; systematic reviews; evidence based practice; oral health

Introduction

The Cochrane Collaboration started in 1993 with the following aim 'Improving healthcare decision-making globally, through systematic reviews of the effects of healthcare interventions, published in The Cochrane Library' (The Cochrane Collaboration). This article will cover some background information about the Cochrane Collaboration and in particular The Cochrane Oral Health Group (COHG) in terms of its structure, editorial processes and the position of the group within the collaboration.

The article will illustrate how Cochrane reviews on oral diseases have contributed to guideline developments internationally. Other example of areas of uncertainty found in Cochrane reviews have led to the commissioning of trials nationally and the results of these trials have been or will be included in the updates of the reviews sometimes leading to a change in the recommendations from one of uncertainty to one of a benefit.

There are challenges in the management of oral diseases in particular head and neck cancer and this article will update readers into how the COHG is undertaking reviews in this area and possible future collaboration with the Cochrane Ear Nose and Throat Disorders group in undertaking the head and neck cancer reviews.

A new initiative for The Cochrane Collaboration is undertaking diagnostic test accuracy reviews and readers will be updated on future reviews in the area to be undertaken by the COHG.

Cochrane Oral Health Group

The Cochrane Collaboration is an 'international not-for-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide' (The Cochrane Collaboration). Its primary function is the production and dissemination of high quality systematic reviews of healthcare interventions. The rationale for systematic reviews has been well documented over the years (Mulrow, 1994; Chalmers and Altman, 1995). Simply, they aim to reduce the ever-increasing volume of both published and unpublished research literature on a specific topic into manageable, unbiased, quality assessed portions.

The Cochrane Collaboration is made up of over 50 Review Groups, of which the COHG is one. Originally established in 1994 in the USA by Alexia Antczak Bouckoms, the editorial base for the COHG transferred to the School of Dentistry, University of Manchester, UK in 1996 with Professors Bill Shaw and Helen Worthington as Co-ordinating Editors. Professor Shaw stepped down as Co-ordinating Editor in 2008, to be replaced by Professor Jan Clarkson. Funding for core

Correspondence: HV Worthington, Cochrane Oral Health Group, School of Dentistry, The University of Manchester M15 6FH, UK. Tel: +44 161 275 7819, Fax: +44 161 275 7815, E-mail: helen.worthington@manchester.ac.uk
Received 17 November 2009; accepted 18 November 2009

staff at the Editorial base is provided by the UK's Department of Health; the Collaboration as a whole, relies entirely on grants and donations and does not accept conflicted funding.

Over the last 15 years the COHG has developed as an extremely productive, international network of health care practitioners, decision makers, researchers and consumers. The aim of the group is, primarily, to produce systematic reviews of randomised controlled trials focusing on the prevention, treatment and rehabilitation of oral, dental and craniofacial diseases and disorders. Many of these reviews are undertaken by highly motivated volunteers, keen to find 'the answer' to a question that is of clinical relevance to them. They are supported throughout the process by the Editorial team who are able to provide clinical, statistical, methodological and technical advice as required.

The COHG aims to have a transparent, rigorous Editorial process (see Figure 1) that ensures all registered review titles, protocols and completed reviews go through extensive peer review. The Managing Editor for the COHG is responsible for co-ordinating the whole process, the key elements of which involve Title Registration, requiring potential authors to provide justification for the chosen topic, details of the proposed review team including their experience of systematic review methodology, and an indication of training needs. Once a title has been approved, the review team are required to develop a detailed protocol (with training available in the form of the Cochrane workshop on Developing a Protocol). The protocol undergoes peer review by the Editorial team and selected external referees prior to publication on the Cochrane Database of Systematic Reviews (CDSR), one of several databases on The Cochrane Library. The assigned Contact Editor for the review liaises with the authors to ensure all relevant comments are addressed. By publishing the protocol the Collaboration aim to reduce bias in the review process by allowing readers across the world to comment on the methods to be used. Once a protocol has been accepted for publication, authors undertake the systematic review according to the methods described. The Editorial team are available to provide advice and support throughout the review process and authors encouraged to attend the Cochrane Analysis workshop. The completed review will, again, undergo further, thorough rounds of both internal and external peer review comments which can be discussed with the Contact Editor. The process does not end with the completion of the full systematic review; Cochrane Reviews are 'living' documents that are updated at regular intervals. Typically this could be every 2 years, but may depend upon the volume and clinical relevance of the emerging research.

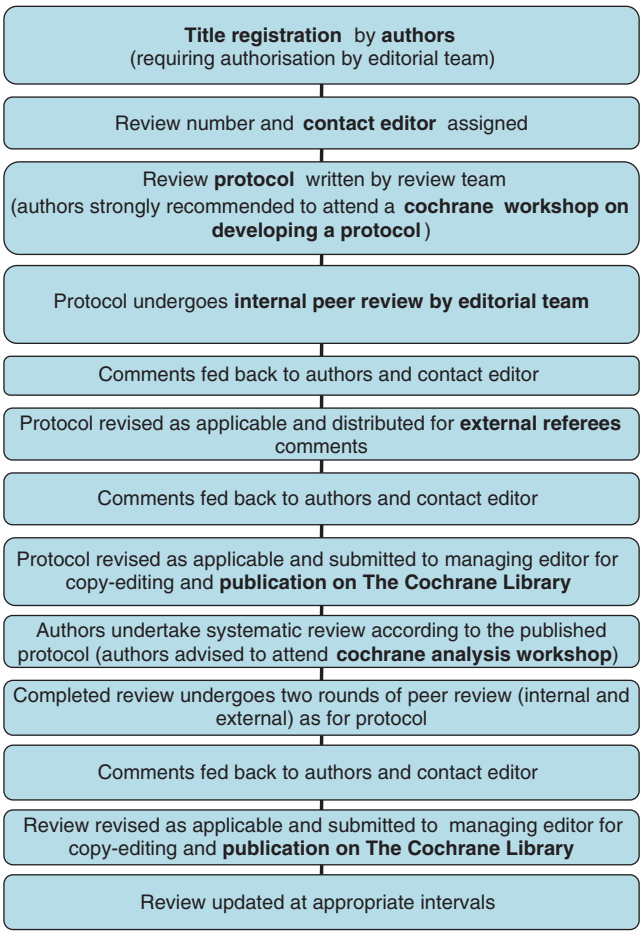

Figure 1 Structured editorial process

In addition to the production of systematic reviews for the CDSR, the COHG is responsible for maintaining a Trials Register of reports of controlled clinical trials (CCTs) and randomised controlled trials (RCTs) relating to oral health. The content of the register is the product of comprehensive electronic searching and handsearching, identifying both published and unpublished reports of trials. The number of reports currently listed in the register is approaching 25 000, making the register a highly valuable resource for all those wishing to identify RCTs/CCTs of oral health. New records added to the Trials Register are updated quarterly to CENTRAL, a database of clinical trials also published on The Cochrane Library.

In addition to CDSR and CENTRAL, The Cochrane Library publishes five further databases (listed in Figure 2). The Library is published quarterly by Wiley InterScience. It is available on a subscription basis online or on DVD-ROM. Individual reviews are also

Cochrane database of systematic reviews (CDSR; cochrane reviews)

Database of abstracts of reviews of effects (DARE; other systematic reviews)

Cochrane central register of controlled trials (CENTRAL; clinical trials)

Cochrane methodology register (CMR; methods studies)

Health technology assessment database (HTA; technology assessments)

NHS economic evaluation database (NHSEED; economic evaluations)

About the cochrane collaboration (about; cochrane groups)

Figure 2 Databases included in The Cochrane Library

available on a pay-per-view basis. Residents in a number of countries or regions can access The Cochrane Library online for free through a 'provision' or a special scheme, including Australia, parts of Canada and the United States, Denmark, Finland, India, Ireland, Latin America and the Caribbean, Norway, Spain, Sweden, New Zealand and the United Kingdom. The Cochrane Library is also available free of charge to all residents of countries in the World Bank's list of low-income economies. Recent developments have included the production of audio summaries or podcasts of selected reviews from The Cochrane Library and the initiation of the Cochrane Journal Club (http://www.cochranejournalclub.com), both of which aim to further promote the work of The Cochrane Collaboration. There is now an application for abbreviated versions of The Cochrane Library to be on accessed on a mobile phone and future training will be delivered on line.

Cochrane reviews in the management of oral diseases due to cancer treatments

The Cochrane review on 'Prevention of oral mucositis or oral candidiasis for patients with cancer receiving chemotherapy (excluding head and neck cancer)' was the second review published on The Cochrane Library by the COHG (Clarkson *et al*, 2000). This review was then expanded to include patients receiving all cancer treatments and divided into two reviews for the 2003 update, one concerned with the prevention of mucositis, and one the prevention of candidiasis. To give readers a sense of the scale of these reviews the initial review included 38 trials (Clarkson *et al*, 2000) and the review solely concerned with the prevention of mucositis published in 2003 included 52 trials, the update in 2006 included 71 trials and the update in 2007, 89 trials (Worthington *et al*, 2007). This review is currently being updated for publication in 2010 and will include over 120 trials.

These substantial reviews formed the start of a series of reviews around the management of oral problems due to cancer treatments as listed below:

- Prevention of mucositis (89 trials; 75 523 patients) (Worthington *et al*, 2007)
- Treatment of mucositis (26 trials; 1353 patients) (Clarkson *et al*, 2007)
- Prevention of candidiasis (28 trials; 4226 patients) (Clarkson *et al*, 2007)
- Treatment of candidiasis (nine trials; 658 patients) (Worthington *et al*, 2007)
- Prevention and treatment of herpes simplex virus (17 trials; 1054 patients) (Glenny *et al*, 2009)

In total 169 randomised controlled trials (82 814 patients) are currently included in this evidence base for the management of these oral conditions.

In 2001 a subcommittee of the United Kingdom Children's Cancer Study Group (UKCCSG) and the Paediatric Oncology Nurses Forum (PONF) was established and designated the UKCCSG-PONF Mouth Care Group. The aim was to produce comprehensive evidence based guideline on mouthcare for the children and young people being treated for cancer. The guideline was informed by the results of the Cochrane reviews (Glenny *et al*, 2006). Prior to the development of the guideline a baseline survey of all 22 UKCCSG centres was undertaken. Its aim was to establish current UK oral care practice for children with cancer. A telephone survey was undertaken with nineteen (86%) of the centres reporting using guidelines/protocols for mouth care (Glenny *et al*, 2004). The use of routine preventive oral care therapies showed the greatest variation between centres. Four centres (18%) did not use any prophylactic oral care therapy other than basic oral hygiene, whereas seven (32%) routinely used a combination of three or more agents. Chlorhexidine was the most frequently administered prophylactic therapy (17/22 centres, 77%), followed by nystatin (11/22 centres). The prevention of candidiasis and mucositis reviews (published since 2000) concluded that there was no evidence for the use of chlorhexidine or nystatin.

The guideline was published in 2006 (Glenny *et al*, 2006) and we conducted a follow-up survey in 2008 which showed that the number of units now using chlorhexidine was 9/21 (six of these centres using it in high risk or neutropenic patients only) and nystatin 2/21. We are currently updating the guideline which will be published in 2010.

Cochrane review on Bell's palsy

Bell's palsy is an acute unilateral paralysis of the facial nerve first described in a paper to The Royal Society in 1821 by the Scottish surgeon Sir Charles Bell (1774–1842). Its cause is unknown but animal studies have suggested the possibility that reactivation of herpes viruses may be responsible for demyelination. It affects 25–35 people per 100 000 in the population per annum, most commonly in the age group 30–45. The condition presents disproportionately amongst pregnant women and people who have diabetes, influenza, a cold, or some other upper respiratory ailment. On average every year a General Practitioner will see one or two patients who have developed the condition. A recent UK study using the general practice research database (GPRD) showed that 36% of patients were treated with oral steroids and 19% were referred to hospital (Rowlands *et al*, 2002). Although most recover well, 30% of patients have a poor recovery with continuing facial disfigurement, psychological difficulties and sometimes facial pain (though the presence and course of pain is unclear from current knowledge). In the absence of an established aetiology, treatment continues to be based upon the established pathophysiology: swelling and entrapment of the nerve.

Two Cochrane reviews concerning the treatment of Bell's palsy have examined the effectiveness of oral prednisolone and aciclovir (Sipe and Dunn, 2001; Salinas *et al*, 2002). These found that insufficient data exist to conclude that either or both therapies are effective. Many of the studies included in the reviews either failed to randomise patients or, when correctly randomised, were erroneously interpreted in a favourable light. In addition

high dose steroid therapy has numerous potential side effects including peptic ulceration hypertension and confusional states. Antiviral therapy is expensive and should be reserved for circumstances where definite benefits are likely to be obtained. Current recommendations suggest that aciclovir needs to be started within 48 h, though more recent studies of viral replication in patients with Bell's palsy suggest that this might be extended.

Given this lack of evidence the UK NHS R&D National Coordinating Centre for Health Technology Assessment (NCCHTA) commissioned an independent academic group to conduct an RCT to determine whether prednisolone or aciclovir, used separately or in combination and used early in the course of Bell's palsy, improved the chances of recovery at 3 and 9 months. With this defined as the primary research question, the protocol for the Scottish Bell's Palsy Study was developed, approved and funded, and the trial was delivered from November 2003 to March 2007, with publication of results achieved in October 2007 (Sullivan *et al*, 2007). The study supported the early use of oral prednisolone in Bell's palsy as an effective and cost-effective treatment, but showed no effect for aciclovir, either alone or in combination with prednisolone.

Following the appearance of these results, a team essentially comprising the Scottish researchers were invited to submit an update to the Cochrane review on Antivirals for Bell's palsy which appeared in October 2009 (Lockhart, 2009). This updated review provided high quality evidence that antivirals are no more effective than placebo (dummy) treatment in producing complete recovery from Bell's Palsy. The review also suggested that corticosteroids might be effective but this conclusion requires confirmation from the Cochrane review of corticosteroids which is being updated.

Cochrane review on recall intervals between routine appointments

In 2002 the National Institute for Health and Clinical Excellence (NICE) in the UK undertook a guideline on what the recall interval between routine dental examinations should be for both adults and children. This includes examination of the mouth for all oral diseases. A Cochrane review on this topic was conducted alongside the guideline and the guideline was published in 2004 (Pitts *et al*, 2004; Beirne *et al*, 2005). The guideline influenced new contracts being issued for National Health Service Dentists working in England and Wales. One of the recommendations of the guideline was the use of a risk based recall interval which would be a joint decision between the dentist and the patient, based on the patient's own personal risk of future disease. As there is still uncertainty with no good quality evidence in the Cochrane review, the National Institute for Health Research in the UK has commissioned a trial to examine the use of a risk based interval compared to fixed intervals of 6 and 12 months. The funding is initially for a feasibility study starting in 2009 and if this is successful a full 3-year trial will be conducted by researchers in Universities of Dundee, Aberdeen, Manchester, Birmingham, Newcastle, Glasgow, Edinburgh, St Andrew's, Amsterdam and The Eastman Dental Institute. The result of this trial will feedback into the update of the Cochrane review and will provide international evidence on what the 'best' recall interval.

Cochrane reviews on head and neck cancer

In 2003 the COHG obtained a USA National Institute of Health grant to undertake a series of Cochrane reviews on the treatment of oral cancer. We were able to fund a research fellow for 2 years to undertake the reviews. After great discussion we decided to undertake four reviews, one for each of surgery, chemotherapy, radiotherapy and immunotherapy. This meant that although many of the trials would be included in more than one review, the focus of each review would be different. We decided to include trials which included over 50% of the patients with oral cancer, rather than simply head and neck cancer. A single protocol for all the reviews was published in 2005, followed by protocols for all four individual reviews published on The Cochrane Library in 2007.

The surgery review was published in 2007 (Oliver *et al*, 2007) and included 31 trials and the authors conclusion was 'There is some evidence that concomitant radio/chemotherapy (with surgery) is more effective than radiotherapy (with surgery) and may benefit outcomes in patients with more advanced oral and oropharyngeal cancers. As these trials were based on head and neck studies, future studies should evaluate this treatment regimen specifically in oral and oropharyngeal cancers separately and also address tumour staging and its impact on outcomes'. The conduct of the chemotherapy and radiotherapy reviews is well underway and we expect to publish these reviews in 2010. Substantially more trials (> 100) will be included in each of these reviews

The COHG are involved on a UK National Institute of Health Research programme grant titled 'Evidence based health care for major congenital and acquired problems of the head and neck' which commenced in 2009. In collaboration with the Cochrane Ear Nose and Throat Disorders Group we intend to expand our reviews on oral cancer to look at the treatment of all head and neck cancers.

Future Cochrane diagnostic test reviews

A new venture for The Cochrane Collaboration and the COHG is conducting reviews of diagnostic test accuracy. The Collaboration have acquired funding to develop methods for undertaking these reviews and have trained many of the review groups (including the Oral Health Group) into these new methods. One of the initial areas which the Cochrane Oral Health Group will be focusing on is diagnostic test accuracy reviews for screening for oral cancer. This fits in well with the American Dental Association's current document 'Research of importance to the practicing dentist, 2009–2010'. The

following is issued as a priority topic in Goal 2, 'Evaluate emerging oral cancer diagnostic methods and devices compared to a well-conducted oral cancer exam and the value of diagnostic, adjunctive and/or screening tests for oral cancer'.

Conclusion

We hope this article has given readers information on the work of the Cochrane Oral Health Group and insight into the diversity of Cochrane reviews in oral diseases. As can be seen here the reviews are successfully being used to change practice and as background for the funding of large scale clinical trials and programmes of research.

The Oral Health Group currently has 100 reviews, 74 protocols published on The Cochrane Library. For a full list of all our reviews please visit http://www.ohg.cochrane.org/

References

Beirne P, Forgie A, Clarkson J (2005). Recall intervals for oral health in primary care patients. *Cochrane Database Syst Rev* Issue 2. Art. No.: CD004346. doi:10.1002/14651858.CD004346.pub2.

Chalmers I, Altman D (1995). *Systematic reviews*. BMJ Publishing Group: London.

Clarkson J, Worthington H, Eden O (2000). Prevention of oral mucositis or oral candidiasis for patients with cancer receiving chemotherapy (excluding head and neck cancer). *Cochrane Database Syst Rev* (2):CD000978.

Clarkson J, Worthington H, Eden T (2007a). Interventions for preventing oral candidiasis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* Issue 1. Art. No.: CD003807. doi:10.1002/14651858.CD003807.pub3.

Clarkson J, Worthington H, Eden T (2007b). Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* Issue 2. Art. No.: CD001973. doi:10.1002/14651858.CD001973.pub3.

Clinical Guideline 19 (October 2004). Dental Recall: recall interval between routine dental examinations. National Institute for Clinical Excellence (NICE), Department of Health, London. www.nice.org.uk/CG019NICEguideline, ISBN: 1-84257-801-4 NICE Clinical Guideline.

Glenny AM, Gibson F, Auld E *et al* (2004). A survey of current practice with regard to oral care for children being treated for cancer. *Eur J Cancer* **40:** 1217–1224.

Glenny A, Gibson F, Auld E *et al* (2006). *Mouth care for children and young people with cancer: evidence-based guidelines*. UKCCSG: Leicester, UK. Available from http://www.cclg.org.uk.

Glenny A, Fernandez Mauleffinch L, Pavitt S, Walsh T (2009). Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer. *Cochrane Database Syst Rev* Issue 1. Art. No.: CD006706. doi:10.1002/14651858.CD006706.pub2.

Lockhart P, Daly F, Pitkethly M, Comerford N, Sullivan F (2009). Antiviral treatment for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* Issue 4: CD001869.

Mulrow C (1994). Rationale for systematic reviews. *BMJ* **309:** 597–599.

Oliver R, Clarkson J, Conway D *et al* (2007). Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. *Cochrane Database Syst Rev* Issue 4. Art. No.: CD006205. doi:10.1002/14651858.CD006205.pub2.

Rowlands S, Hooper R, Hughes R, Burney P (2002). The epidemiology and treatment of Bell's palsy in the UK. *Eur J Neurol* **91:** 63–67.

Salinas R, Alvarez G, Alvarez M, Ferreira J (2002). Corticosteroids for Bell's Palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* Issue 1: CD001942.

Sipe J, Dunn L (2001). Aciclovir for Bell's Palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* Issue 4: CD001869.

Sullivan F, Swan I, Donnan P *et al* (2007). Early treatment with prednisolone or acyclovir in Bell's Palsy. *N Engl J Med* **357:** 1598–1607.

The Cochrane Collaboration. The reliable source of evidence in health care. Retrieved 28 October, 2009, from http://www.cochrane.org/.

Worthington H, Clarkson J, Eden T (2007a). Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* Issue 4. Art. No.: CD000978. DOI: 10.1002/14651858.CD000978.pub3.

Worthington H, Clarkson J, Eden T (2007b). Interventions for treating oral candidiasis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* 2007. Issue 2. Art. No.: CD001972. doi:10.1002/14651858.CD001972.pub3.