PostScript

LETTERS

The Cochrane review on nicotine replacement therapy: incorrect or uncertain classifications of additional support levels

The Cochrane review of nicotine replacement therapy (NRT) has concluded that the effectiveness of NRT seems to be largely independent of the intensity of additional support provided to the smoker.¹ In fact, trends in their data indicate that NRT had a relatively greater effect (higher odds ratios favouring treatment) when given with minimal support, even though the absolute increase in abstinence rates was larger when combined with high-intensity support.

In the Cochrane review,¹ low-intensity additional support was regarded as part of the provision of routine care. If the duration of time spent with the smoker (including assessment for the trial) exceeded 30 min at the initial consultation or the number of further assessment and reinforcement visits exceeded two, the level of additional support was categorised as high. Categorisations were based predominantly on published reports.

While examining NRT trials involving community volunteers for another project, I noted apparent anomalies in support level classifications of the Cochrane review.¹ A systematic examination of adjunctive treatment of the 14 English language, community volunteer smoking cessation trials listed in the Cochrane review, which included a placebo or no NRT condition and which were categorised as low support was then undertaken.

In 6 (43%) trials, published descriptions supported the Cochrane review classification as low-level support and 3 (21%) trials²⁻⁴ did clearly not appear to satisfy the Cochrane review criteria. In 5 (36%) trials,⁵⁻⁹ lack of a Cochrane definition concerning what constitutes reinforcement or lack of explicit detail in the study publication raised considerable uncertainties about their classification as low support. The lack of information about behavioural counselling is a common void in NRT studies and meta-analyses.¹⁰ Table 1 contains adjunctive support descriptions in the eight trials that did not clearly meet low-level support criteria.

Less than half of the Cochrane review¹ low support classifications were clearly supported by data in the published reports, based on the review's own stated criteria. This finding casts doubt on the validity of conclusions reached about the effectiveness of low versus high additional support.

Attempted contacts with first authors of the five trials⁵⁻⁹ in the uncertain category to clarify intervention details indicate the percentage of incorrect classifications by the Cochrane review¹ is higher than the figure based solely on published data. Although three authors either could not be contacted or were unable to provide requested data, the information supplied demonstrated that two studies did not satisfy the low-intensity support criteria. In one study⁷ (Killen J, personal communication, 2006), the duration of the first visit exceeded 30 min for

Table 1 The Cochrane review of nicotine replacement therapy community volunteer trials incorrectly or uncertainly classified as low-level support. Published details of adjunctive treatment/reinforcement

Authors, year	Adjunctive treatment and reinforcement descriptions in published reports
Trials incorrectly classified	
Jarvik and Schneider, 1984	Volunteers returned daily in the first week for assessment and 30 min of individual clinic support. Seven further visits included clinic support
Clavel <i>et al</i> , 1985	Volunteers received three 1 h group therapy sessions during first month
Tonnesen <i>et al</i> , 1991	Seven visits each lasting approximately 20-60 min. Each visit included a few min of cessation advice and patch explanations
Trials uncertainly classified	
Areechon and Punnotok, 1988	First visit included a lecture on the benefits of cessation of an unspecified duration. Weekly consultations with physician, unspecified content, duration and number
Daughton <i>et al</i> ,* 1991	First visit included medical history, physical examination, smoking history, ECG, taking blood and urine samples and the Fagerstrom questionnaire and also, at site A, brief individual counselling with negotiation of quit date, unspecified content and duration. At site B the first of two group lectures, unspecified content and duration. No details of any verbal patch instructions. Subsequently, participants maintained daily diary for 4 weeks, returned for weekly adverse event review and received low-intervention counselling in the final 2 weeks, unspecified content and duration
Killen <i>et al</i> ,*1997	First visit included measurements of craving, depression and body mass index, completion of a plan of action where patients detailed three risk situations and at least one coping strategy for each, self-help manual and patch instruction; and half of the participants watched 20-min video in groups and received instructions to use video, unspecified duration of non-video component
Davidson <i>et al</i> ,*1998	First visit included motivational questionnaire, setting quit date, brief medical history, medication list, smoking history, CO measurement, patch application instructions, supervised patch application, smoking diary introduction and provision of self-help booklet. At each of six weekly return visits during patch therapy, volunteers' smoking-diary cards and adverse events were reviewed, CO levels were monitored, patients underwent drug accountability procedures including signing logbook and collected an additional 7-day supply of patches, unspecified duration of first visit.
Tonnesen <i>et al</i> , 1999	Multicentre trial: duration of time volunteers spent in clinics at different centres ranged from 10 to >30 min, however, it is not explicitly stated if this is for all visits combined or for each visit. Eight return visits; training protocol provided "detailed guidelines about verbal information and support at each visit...", unspecified content and duration of required supportive follow-ups.

CO, carbon monoxide.

*Comprehensive first-visit details provided for three studies in which duration was not specified in the publication, but description suggested may have exceeded 30 min.

subjects in the video-enhanced group (half of total participants), and in a second study⁹ (Tonnesen P, personal communication, 2006), there were eight reinforcement visits, each of which included medication advice and counselling of approximately 5 min duration.

It is recommended that the authors of the Cochrane review¹ should recode levels of support and provide a definition of what constitutes reinforcement in future editions, and that the support-level classification "not stated" be used more frequently when contact with authors fails to resolve uncertainties in the published report. At the least, all 35 studies classified as low-intensity support should be recoded, not just the subsample of community studies reassessed by myself. Ideally, the 65 studies classified as high-intensity support should also be recoded.

Finally, the reviewers should reanalyse their data to determine whether the recoding process has any substantive impact on the odds ratio comparing levels of additional support or on the absolute increases in abstinence rates in the different support level categories. Such reanalyses are beyond the length and scope of this letter.

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doi: 10.1136/tc.2006.018507

Competing interests: None.

References

- 1 Silagy C, Lancaster T, Stead L, *et al*. Nicotine replacement therapy for smoking cessation (Cochrane Review). In: *Cochrane Library*, Issue 3, 2004; Oxford, 2000, CD000146.
- 2 Jarvik ME, Schneider NG. Degree of addiction and effectiveness of nicotine gum therapy for smoking. *Am J Psychiatry* 1984;**141**:790-1.
- 3 Clavel F, Benhamou S, Company-Huertas A, *et al*. Helping people to stop smoking: randomised comparison of groups being treated with acupuncture and nicotine gum with control group. *BMJ* 1985;**291**:1538-9.
- 4 Tonnesen P, Norregaard J, Simonsen K, *et al*. A double-blind trial of a 16 hour transdermal nicotine

- patch in smoking cessation. *N Engl J Med* 1991;**325**:311–15.
- 5 Areechon W, Punnotok J. Smoking cessation through use of nicotine chewing gum: a double-blind trial in Thailand. *Clin Ther* 1988;**10**:183–6.
 - 6 Daughton DM, Heatley SA, Prendergast JJ, et al. Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1991;**151**:749–52.
 - 7 Killen JD, Fortmann SP, Davis L, et al. Nicotine patch and self-help video for cigarette smoking cessation. *J Consult Clin Psychol* 1997;**65**:663–72.
 - 8 Davidson M, Epstein M, Burt R, et al. Efficacy and safety of an over-the-counter transdermal nicotine patch as an aid for smoking cessation. *Arch Fam Med* 1998;**7**:569–74.
 - 9 Tonnesen P, Paoletti P, Gustavsson G, et al. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. *Eur Respir J* 1999;**13**:238–46.
 - 10 Murray RP, Anthonisen NR. Interventions for smoking cessation: the outcomes are determined by the questions asked. *Eur Res J* 1999;**13**:231–2.

Authors' response

We are grateful to Dr Walsh for pointing out the misclassification of trials in the low-intensity subgroup of the Cochrane review.¹ We agree with him that three trials were incorrectly classified.^{2–4} The intention of the low-intensity classification was to identify an amount of support that might realistically be provided within usual care, both in terms of the initial contact time and the amount of follow-up, but the cut-offs were somewhat arbitrary, particularly for the follow-ups. Given the lack of evidence for effective relapse prevention interventions,⁵ we do not think it likely, however, that differences in the number of brief contacts, given to both active and placebo participants, would substantially modify the relative treatment effect.

Of the trials in the uncertain group, we agree that Areechon and Punnotok⁶ could be regarded as high intensity because the weekly consultations with a doctor seem to have continued over an extended period. Daughton *et al*⁷ is problematic because the brief counselling at site A might be regarded as part of normal care but two group lectures would not. We think that both arms of the factorial trial reported by Killen *et al*⁸ fall into the low-intensity category. In fact, the odds ratio (OR) for the effect of nicotine gum in the video arm was <1 so reclassifying it would increase the low-intensity point estimate. The study by Davidson *et al*⁹ was designed to be a trial of an over-the-counter nicotine patch and

although there were weekly visits to collect patches and for data collection, we think it would be perverse to regard it as high intensity. The Collaborative European Anti-Smoking Evaluation Trial¹⁰ likewise involved relatively brief advice. Although eight return visits were scheduled these were widely spaced, and only three were scheduled within the first 4 weeks.

In the subgroup analysis, comparison 03 in the Cochrane review, we classified 34 trials as offering low-intensity support, and 66 as offering high-intensity support. The low-intensity group included 21 trials of nicotine gum and 13 of nicotine patch. One of the patch trials had a factorial design,⁸ as already noted, and was treated as two studies in the meta-analysis. The OR for the low-intensity studies was 1.81 (95% confidence interval 1.61 to 2.02). Excluding the three misclassified studies led to a very small reduction in the OR (1.74, 95% CI 1.55 to 1.95). Excluding these and the uncertain studies has even less impact (OR 1.78, 95% CI 1.55 to 2.04). In this analysis, the estimate for the high-intensity subgroup was almost identical (OR 1.79, 95% CI 1.66 to 1.93).

Dr Walsh was specifically interested in a subset of 14 of the 34 low-intensity studies, those that recruited community volunteers. The other studies in the Cochrane review subgroup were recruited from healthcare settings. When we pooled the six correctly classified community volunteer trials,^{11–16} the overall OR was still similar (OR 1.76, 95% CI 1.32 to 2.35). In the subset of three gum studies, the estimate was no longer significant (OR 1.34 95% CI 0.89 to 2.02), but as the CIs are wide and this was one of multiple post hoc subgroups we do not think this should be interpreted as evidence of no effect for that particular subgroup.

The corrected analysis, which will be published in an update to the Cochrane review, continues to support the conclusion that differences in the common level of support are not important determinants of the relative treatment effect.

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doi: 10.1136/tc.2006.019158

Competing interests: None declared.

References

- 1 Silagy C, Lancaster T, Stead L, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2004;(3):CD00146.
- 2 Jarvik ME, Schneider NG. Degree of addiction and effectiveness of nicotine gum therapy for smoking. *Am J Psychiatry* 1984;**141**:790–1.
- 3 Clavel F, Benhamou S, Company-Huertas A, et al. Helping people to stop smoking: randomised comparison of groups being treated with acupuncture and nicotine gum with control group. *BMJ* 1985;**291**:1538–9.
- 4 Tonnesen P, Norregaard J, Simonsen K, et al. A double-blind trial of a 16 hour transdermal nicotine patch in smoking cessation. *N Engl J Med* 1991;**325**:311–15.
- 5 Hajek P, Stead L, West R, et al. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev* 2005;(1):CD00399.
- 6 Areechon W, Punnotok J. Smoking cessation through use of nicotine chewing gum: a double-blind trial in Thailand. *Clin Ther* 1988;**10**:183–6.
- 7 Daughton DM, Heatley SA, Prendergast JJ, et al. Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Intern Med* 1991;**151**:749–52.
- 8 Killen JD, Fortmann SP, Davis L, et al. Nicotine patch and self-help video for cigarette smoking cessation. *J Consult Clin Psychol* 1997;**65**:663–72.
- 9 Davidson M, Epstein M, Burt R, et al. Efficacy and safety of an over-the-counter transdermal nicotine patch as an aid for smoking cessation. *Arch Fam Med* 1998;**7**:569–74.
- 10 Tonnesen P, Paoletti P, Gustavsson G, et al. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. *Eur Respir J* 1999;**13**:238–46.
- 11 Fortmann SP, Killen JD. Nicotine gum and self-help behavioral treatment for smoking relapse prevention—results from a trial using population-based recruitment. *J Consult Clin Psychol* 1995;**63**:460–8.
- 12 Hughes JR, Gust SW, Keenan RM, et al. Effect of dose on nicotine's reinforcing, withdrawal-suppression and self-reported effects. *J Pharmacol Exp Ther* 1990;**252**:1175–83.
- 13 Schneider NG, Jarvik ME, Forsythe AB, et al. Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial. *Addict Behav* 1983;**8**:253–61.
- 14 Hays JT, Croghan GA, Offord KP, et al. Over-the-counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled and open label trials. *Am J Public Health* 1999;**89**:1701–7.
- 15 Paoletti P, Fornai E, Maggiorini F, et al. Importance of baseline cotinine plasma values in smoking cessation: results from a double blind study with nicotine patch. *Eur Respir J* 1996;**9**:643–51.
- 16 Sonderskov J, Olsen J, Sabroe S, et al. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. *Am J Epidemiol* 1997;**145**:309–18.