Reviewer’s report

Title: Updating systematic reviews - what difference does it make? Case study of nicotine replacement therapy

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Reviewer: Dr Julian Higgins

Level of interest: A paper of limited interest

Advice on publication: Unable to decide on acceptance or rejection until I see revised version

Comments

The updating of systematic reviews is an increasingly important topic in this era of electronic publication, and it has received very little methodological attention. The authors use a systematic review of nicotine replacement therapy as a case study in addressing issues related to updating of reviews. The case study appeared in the Lancet and later in the Cochrane Database of Systematic Reviews (CDSR), where it has been updated over time. The review has always been one of the largest reviews in the CDSR and therefore of interest and worthy of study. A second corollary, however, is that it provides an appropriate basis for generalizations of practical relevance to the vast majority of systematic reviews and reviewers.

The paper lays down its objectives clearly. I have a few concerns over the methodology subsequently employed which appears at times superficial, and over the appropriateness of the conclusions. At times the paper seems to confuse (i) updating meta-analyses with updating reviews; and (ii) updating reviews with performing new studies. My over-riding feeling is that the paper could be revised along one of two alternative lines: either taking a more scientific approach to the objectives presented, or becoming more discursive and addressing practical problems in re-preparing and interpreting updated reviews.

Major comments

1) In order to establish whether there were clinically significant changes, a definition of clinical significance is needed (e.g. how big an odds ratio?). At the most basic level, this may be compared with the confidence intervals. (Ideally, sequential statistical methods would be used.)

2) The paper mixes together issues of updating meta-analyses and updating reviews. The authors’ conclusion for the principle meta-analyses in the review is that they are
conclusive and need not be updated. Their conclusion for the review in general is different. The two issues are somewhat different and they should be better separated in the paper. I consider the review aspects to be more interesting than the meta-analyses, since the authors do not employ proper statistical methods for accumulating evidence over time relative to a clinically worthwhile treatment effect.

3) The ‘Conclusions’ section seems to contradict itself. It addresses (and possibly confuses) two very different issues: that of updating reviews/meta-analyses and that of undertaking or funding further trials. The idea of abandoning one of the key principles of the Cochrane Collaboration (“Keeping up to date”) is a serious turn, and surprising from these particular authors. Are they really contemplating this? Or suggesting it for this particular meta-analysis? (And if so, how in general might one select reviews that one can justifiably stop updating?) To me the important conclusion relates to the undertaking of further trials in this area. However, the authors conclude that new trials are addressing new questions, and so are useful. This leads me to another concern...

4) The notion of the review changing the nature of the questions addressed needs clarifying. I am unsure whether this means (i) changing the objectives of the review or (ii) the accumulation of data that allow original objectives to be addressed. Was/is there a protocol for the review that is being followed? It would be helpful to specify the exact objectives of the NRT review along with its inclusion criteria. I identify two possible scenarios:
Case (i): If the objectives (or inclusion criteria) are being changed, then the paper describes the reviewers’ slightly non-systematic approach to summarizing evidence, and could be a case study in the difficulties of constantly ‘reviewing’ the changing nature of clinical research. (Otherwise it could be about the changing nature of studies being performed, and is of historical interest for trials in nicotine replacement, but not for updating reviews.)
Case (ii): If the nature of available data is altering the review’s ability to answer a set series of questions, then the paper is about issues in the updating of reviews: it concerns the accumulation of evidence relevant to an important clinical question.

5) I think the paper would benefit considerably from a table presenting a direct comparison of the 1994 and 2000 versions of the review (numbers of studies, results presented in the text, questions addressed, etc). I had to draw a table to make sense of the multiple results presented.

6) I would like to see a more detailed discussion of the question posed in the Introduction: “Is there a point in the research process where updating can add nothing further and should be abandoned?” It’s a very difficult one, though! In the conclusions, the authors should not attempt to answer the question “What then does updating achieve?” (though they could answer “What then *did* updating achieve?”), but might consider any general (‘qualitative’) lessons that might be learnt from this case study (e.g. the different dimensions of a review, as highlighted in this paper, makes the question more complex than might first appear).

Minor comments

(Line numbers ignore headings)

7) p.4, line 19-20. The reviewers’ objectives include “To describe...
the nature of the questions addressed by the review”. Please clarify: does this mean changing the objectives of the review by adding additional questions, or acquiring sufficient information to address previously specified questions?

8) p.5, lines 1-5. In their objectives, the authors state that they wish to establish whether significant changes in effectiveness were identified (a) overall and (b) within subgroups. Judging by their use of interaction tests, I wonder whether for the latter they are interested rather in differential effects in the different subgroups?

9) p.5, line 6-7. I am unsure of the relevance of case mix, level of support or length of follow up to the updating process. Please clarify.

10) p.4, line 5. Subgroup analyses are mentioned for exploring heterogeneity. A better method is meta-regression, which can be used both to compare subgroups and to explore numerical characteristics of studies. Could this be mentioned too?

11) p.7, line 7 and 9. The d.f. for the heterogeneity test in the 2000 review is 30, and so is the number of trials. One must be wrong.

12) pages 7 and 8. There is a subheading 'Length of follow-up', but not for Case mix or High/low intensity. This makes the section rather difficult to follow.

13) p.7, line 20-p.8, line 4. The particular discussion of effect sizes in primary care and community trials does not seem relevant to the updating of the review from 1994 to 2000: no comparisons here, and it is not clear to which year the results (ORs 1.47 and 1.86) apply.

14) p.9, line 12-14. While I certainly agree with the point being made, I am slightly uncomfortable with the discussion of possible spurious findings related to behavioural support that were "nullified" in the update. For example, the point estimates for gum were 1994 low: 1.81; high: 1.55 2000 low: 1.72; high: 1.56 These don’t look that different to me. For the patch a "non significant trend" turned into a very similar pair of results. Were the 1994 results over-interpreted by the reviewers at the time?

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Editorial questions

1. Are the conclusions drawn adequately supported by the data shown: if not, what are the shortcomings and could they be overcome?

No. See comments

2. Are sufficient details provided to allow replication of the work or comparison with related analyses?

Yes.

3. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes.

4. Is the writing acceptable?

Yes.

**Competing interests:**

The paper describes work produced by an the Cochrane Collaboration. As an active member of the Collaboration I have received reimbursements for travel and accommodation for attending meetings and contributing to training programmes, and have received a small sum of money for consultancy from an entity within the Collaboration. I have had no financial involvement with the particular entities represented by the authors.