Reviewer's report

Title: Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials

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Reviewer: Peter Lee

Some comments
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Date: 2nd April 2015

The authors describe a systematic review and meta-analysis of RCTs which specifically compare varenicline with nicotine replacement therapy (NRT) with varenicline alone. While the paper is clearly presented and generally well written, I have a number of comments, which I give generally in the order in which they appear in the paper.

1. Though the English is clear enough, there is a tendency to omit the word “the” on some occasions where it should be there.

Examples are:
Abstract line 10 “by the Jadad score” (also p 8 line 8)
p 7 line 10 “by the Boolean operator”

2. On line 12, it is unclear why it says “24 weeks in most studies” when there were only two relevant studies which provided long-term results and 24 weeks was relevant to both. Also, it should be made clear in the abstract that only two studies did. Note also p 8 line 18 where the strange word “majorly” is used.

3. It would be useful in the Background to give summary relative risks (RRs) or odds ratios (ORs) for published meta-analyses of varenicline only or of NRT only (e.g.1-3).

4. I would argue that there is little point in testing for publication bias with only three studies. Is it possible to get significant results?

5. I do not understand why ORs were used in preference to RRs. I thought that ORs were only generally used in case-control studies where the OR is an
approximation to the RR. However, I do note some exceptions in the literature.

6. In Figure 1, I did not understand what “journal select” means in the box “Articles excluded after fuller text review”. Also, in the box, why is an “author manuscript” rejected, and how was it identified in the first place?

7. Table 1 and the associated text give no details on some essential information on the studies – location, population studied, and inclusion/exclusion criteria.

8. Also in Table 1, the word “administrated” might be replaced by “started”.

9. On page 11 line 6 “Three studies with a total of 893 participants” is clearer.

10. I obtained the three relevant source papers in the meta-analysis and carried out my own data extraction and meta-analysis. Although in general I could reproduce the relevant numbers, odds ratios and 95% CIs in Figures 2 and 3 and Table 2, I did note two points:

(a) In the Koegelberg study, the numbers abstinent have been taken from the multiple imputation analysis (MIA) and not from the per-protocol analysis. Certainly, one cannot take the numbers from the MIA into the meta-analysis and assume that the OR, and particularly its variance, would be correct. Using the per-protocol data seems simpler and less open to objection.

(b) Though I can reproduce the ORs and 95% CIs precisely from the data in Figures 2 and 3 (and Table 2), I disagree with the weights. This is strange as the weights are used in producing the combined estimate. For the short-term abstinence, for example, I used the formula for the variance of log OR as 1/A+1/B+1/C+1/D where A, B, C, D are the numbers in the four cells (patch/placebo x quit/not quit) and taking weight as 1/variance I got the absolute weights of 7.03, 26.59 and 19.29 which became weights as %s of 13.28, 50.25 and 36.47 (spreadsheet available on request).

11. Table 2 could usefully include the numbers of cases and ORs/CIs in the individual studies, and results of heterogeneity tests.

Of these points, I would classify 7 and 10 as major compulsory revisions, 1, 2, 6, 8, 9 as minor essential revisions, and 3, 4, 5 and 11 as discretionary revisions.

References


Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I am a long-standing consultant to various tobacco companies