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

Version: 3  Date: 15 May 2015

Reviewer: Bo Zhang

Reviewer’s report:

This study is to investigate the efficacy and safety of varenicline combined with NRT, by conducting a systematic review and meta-analysis of randomized controlled trials (RCTs). Authors searched MEDLINE, EMBASE, ClinicalTrial.gov, and Cochrane Library for relevant RCTs. Two independent authors reviewed and selected RCTs. The quality of RCTs was evaluated by Jadad score. Overall, 3 RCTs with 893 participants were included in the meta-analysis. The study examined both early and late outcomes by combination use of varenicline and NRT and found that the combination therapy is favourable (OR=1.51, 95% CI 1.16-1.98 for early outcome and OR=1.65, 95% CI 1.23-2.23 for late outcome). The study concludes that combination therapy is more effective than varenicline alone, and adverse events of combination therapy are similar to mono-therapy except for skin reactions.

Major Compulsory Revisions

1. The study question is not well defined. This study’s aim is to evaluate the efficacy and safety of varenicline combined with NRT, but only examines the efficacy of varenicline plus NRT compared to varenicline alone, but not to NRT alone. You need to refine your objectives.

2. Generally, the methods are appropriate and well defined. It appears that the study followed the standards for systematic literature review and meta-analysis. The methods include search strategy, selection criteria, quality assessment and publication bias, and statistical analysis. One concern is about its inclusion criteria. Based on the study selection criteria, “published RCTs with an adult population”, “to investigate combination treatment of varenicline and any type of NRT”, “outcomes were abstinence rates with biochemical verification, safety profile”, an RCT by “Varenicline to stop long-term nicotine replacement use: a double-blind, randomized, placebo-controlled trial. Nicotine Tob Res 2013; 15(2):419-27” meet these inclusion criteria. In this trial, all participants with long-term NRT use were randomized to varenicline or placebo for 12 weeks, with 52 week follow-up. This can be taken as an RCT of varenicline plus NRT (any form) vs. NRT alone (any form). This RCT has early and late quit outcomes and adverse events were reported. If the current study is only to compare varenicline plus NRT and varenicline alone, you need to make changes to your inclusion criteria.
3. Figures appear to be genuine. The labels for treatment should be “varenicline plus nicotine patch” and “varenicline plus placebo patch”. Otherwise, the current title seems to compare nicotine patch to placebo patch.

4. The authors appear to adhere to the standards of systematic review and meta-analysis. Their conclusions reflect the analysis well. The issue of small number of trials included in their analysis and limitations of the study are discussed. This study only considers published but not unpublished studies, which are clearly reported. The authors may consider indicating that larger RCTs are needed to make more robust conclusions.

5. The title and abstract generally convey what has been found in this manuscript. However, the statements of the abstract “limited evidence exists regarding whether combination of varenicline and NRT is more effective than either alone. The aim of this research was to investigate the efficacy and safety of varenicline combined with NRT.” seem to compare combination of varenicline and NRT to varenicline alone and to NRT alone. Need to rephrase these statements.

6. It is not clear why “The results suggested the possible additive effect of NRT to varenicline.” (last sentence of the last paragraph of the Background) You need to explain this a bit more.

Minor essential revisions
1. Need to add this. Combination therapy of varenicline with NRT is not recommended either by the US Public Health Clinical Practice Guideline for Treating Tobacco Use and Dependence (your ref #4) (Second paragraph of the Background).

2. Add the Jadad score in Table 1 for each RCT.

Discretionary revisions
1. Consider listing the 7 first-line cessation medications when you mention them (First paragraph of the Background).

2. It is preferable to present data in relative risk over odds ratio for your meta-analysis.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.