Author's response to reviews

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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Author's response to reviews: see over
Cover Letter

Dear reviewers:

Enclosed is one copy of our manuscript, entitled: “Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials.” an original article to be considered for publication in BMC Public Health.

I am very grateful for your comments on our manuscript. According to your advice, we have amended the relevant parts in the manuscript. Some of your questions are answered below.

Response to reviewer Bo Zhang’s report:

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.

Response: Thank you for your kind reminder. We did intend to evaluate the efficacy and safety of combination therapy to varenicline or NRT alone. But after searching for possible RCTs, comparisons were only available in combination therapy versus varenicline alone. No RCT of combination therapy versus NRT alone could fit our inclusion and exclusion criteria.

To increase the understanding of general readers regarding this point, we add some description in the result and the discussion section as the following:
“After review, all three studies [9-11] were finally included in the systematic review and meta-analysis (Tables 1). These three studies were all combination therapy versus varenicline alone therapy trials.”

“Our research identified three smoking cessation trials comparing varenicline combined with nicotine patch versus varenicline combined with placebo patch. No other types of nicotine product were combined with varenicline in these trials. We found no trials comparing combination therapy with NRT alone that met our inclusion and exclusion criteria.”

We also put it in the abstract: “All three were comparing combination therapy with varenicline therapy alone.”

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.

**Response**: We had looked into this trial. Patients in this trial were recommended to stop NRT use between the first and second week of the treatment in both arms. The dose, form and the continuity of NRT varies both in treatment and control groups. Some patients in the combination therapy group actually use combination therapy only for one to two weeks, then they could stop NRT and keep varenicline alone. The intention of this trial was to investigate whether varenicline could stop long-term NRT, but not to evaluate the efficacy of varenicline plus NRT. The aim was different from our study and other included trials in the first place. It was indeed a combination therapy, but not the one we’re looking for. By adding this trial, we believed that heterogeneity would increase, and the conclusion would not be made more clear. However, it’s true that in our original manuscript the inclusion criteria did not clearly rule out this trial. We refined the inclusion criteria and also described the reason why this trial was not added in the method section (P. 8) as the following:

“Exclusion criteria included non-RCT studies, trials without outcome measurements, trials using smoking cessation medications but not aiming to stop cigarette smoking (eg. stop alcohol use or long term NRT use), and articles that the full-text was not available.”

We also added description of this trial in the discussion section (P. 14):

“One RCT that compared combination therapy and NRT was not included because it combined varenicline and counseling to get long-term NRT users to quit NRT [17].”
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.

Response: Thank you for the concern of misunderstanding. However, we prefer to retain the current format due to two reasons: First, the titles of Figure 2 and 3 are already “Varenicline Plus Nicotine Patch vs Varenicline Plus Placebo Patch”, so when the readers read the title first they should not be confused. Secondly, the space left for the legend is limited so we arranged our wording to fit in one line so that the figure is more comprehensible.

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.

Response: Thank you. We added that in our conclusion according to your advice:

“The combination therapy of varenicline with NRT is more effective than varenicline alone in smoking cessation. This effect is more evident if pre-cessation treatment of nicotine patch is administrated. The adverse events of combination therapy are comparable to varenicline mono-therapy with the exception of skin reactions. 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.

Response: As mentioned above, we did intend to evaluate the efficacy and safety of combination therapy to varenicline or NRT alone. But after searching for possible RCTs, comparisons were only available in combination therapy versus varenicline alone. No RCT of combination therapy versus NRT alone could fit our inclusion criteria. We added this in the result and the discussion section, and also in the abstract.

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.

Response: It was further explained and discussed in the fourth paragraph of “Discussion.” It indeed seemed a redundant and undefined phrase here, so we decided to just remove it. Thank you very much for your advice. The explanation of this phrase in the discussion part was as the following:

“The rationale of combination therapy of varenicline with NRT resides in the hypotheses that 1) varenicline does not fully saturate α4β2 nicotinic acetylcholine receptors; 2) varenicline does not completely replace the dopaminergic effect of smoking [29]. A standard-dose of varenicline (1.0mg) could achieve higher abstinence rates than low-dose varenicline (0.5mg) [3]. Further
saturation of the receptors seemed to explain the additive effect of NRT. However, a neuropharmacological study utilizing positron emission tomography revealed that a single dose of 0.5mg varenicline could saturate $\alpha_4\beta_2$ receptors in the human brain [30]. It deserves a debate whether the combination to $\alpha_4\beta_2$ nicotinic acetylcholine receptors, and subsequent mesolimbic dopamine release is the only pathway that causes reward in smoking. Nicotine addiction develops from complex pathways, and individual genotypes influence both smoking behavior and treatment effects [31, 32].”

Minor essential revisions

7. 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).

Response: Thank you, we added it in our revised manuscript as the following:

“Combination therapy of varenicline with other medications was not recommended in the guideline proposed by the National Institute for Health and Care Excellence (NICE) [7]. Combination therapy of varenicline with NRT is not recommended either by the US Public Health Clinical Practice Guideline for Treating Tobacco Use and Dependence [4].”

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

Response: Thank you, we added Jadad score in Table 1 for each RCT.

Discretionary revisions

9. Consider listing the 7 first-line cessation medications when you mention them. (First paragraph
Response: We added the 7 first-line cessation medications in the background section as the following (P. 6):

“In a guideline proposed to treat tobacco use and dependence in 2008, seven first-line medications were recommended (nicotine in the forms of gum, inhaler, lozenge, nasal spray and patch, sustained release bupropion hydrochloride, and varenicline) [4]. Among them, varenicline had the highest abstinence rate.”

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

Response: We are aware that there are debates of using either relative risk or odds ratio in a meta-analysis. Both have been used in previous published researches. One important meta-analysis about smoking cessation medications even used both relative risk and odds ratio in the paper. (Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Reviews. http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD009329.pub2 ). To avoid the debates, we chose the default method of RevMan, the Mantel-Haenszel odds ratio. Because we did not prefer odds ratio or relative risk in the first place, we did not change the default setting. We believe those who prefer one over the other have to address their specific reason against the use of the other. If there is not a strong reason against using odds ratio, please allow us to use this default method in RevMan.

In a study comparing 551 systemic reviews, there was no difference on average between RR and
Response to reviewer Peter Lee’s report:

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

   **Response:** We looked into our manuscript again and corrected some grammar errors, including the lack of the “the” problems. Thank you very much.

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.*

   **Response:** We re-organized the sentences to make it more clear for the readers. The re-organized parts were as the following:

   The result section of the abstract: “Three randomized controlled trials with 904 participants were included in this meta-analysis. All three were comparing combination therapy with varenicline therapy alone. The late outcomes were assessed in 2 of the 3 trials. Both the early and late outcomes were favorable for combination therapy (OR = 1.50, 95% CI 1.14 to 1.97; OR = 1.62, 95% CI 1.18 to 2.23, respectively).”

   The method > statistical analysis section: “The late outcome was the abstinence rate assessed after the end of treatment completion, at 24 or more weeks after the target quit date (TQD).”

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).*
Response: Thanks for your advice. We added RRs and ORs for published meta-analyses in our revised manuscript as the following:

“A meta-analysis revealed that varenicline was more effective than standard-dose nicotine replacement therapy (NRT) (relative risk = 1.38, 95% CI 1.15 to 1.64 at 6 months), but was similar to high-dose NRT (relative risk = 1.05, 95% CI 0.80 to 1.36 at 6 months) [5]. In another meta-analysis, although varenicline was still regarded as the most effective mono-therapy, it was not superior to combination therapy of two different types of NRT [odds ratio (OR) = 1.06, 95% CI 0.75 to 1.48] [6].”

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?

Response: With only 3 trials included, it might seem to be pointless to perform testing for publication bias. But we do not know how many trials could be identified before we actually started the search. It served as one part of the standard study design and helped maintain our study quality. So we think it is better to keep this test in the article.

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.

Response: Odds ratio is not only used in case-controlled studies, many clinical trials also use odds ratio. In our meta-analysis, two of the three included RCTs used odds ratio to analyze the results.
We are aware that there are debates of using either relative risk or odds ratio in a meta-analysis. Both have been used in previous published researches. One important meta-analysis about smoking cessation medications even used both relative risk and odds ratio in the paper. (Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Reviews. http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD009329.pub2 ). To avoid the debates, we chose the default method of RevMan, the Mantel-Haenszel odds ratio. Because we did not prefer odds ratio or relative risk in the first place, we did not change the default setting. We believe those who prefer one over the other have to address their specific reason against the use of the other. If there is not a strong reason against using odds ratio, please allow us to use this default method in RevMan.

In a study comparing 551 systemic reviews, there was no difference on average between RR and OR regarding consistency. (Jonathan J. Deeks. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. Statist. Med. 2002;21:1575–1600. DOI: 10.1002/sim.1188).

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?

Response: We are sorry there were confusing terms in Figure 1 due to Chinese translation. We rearranged the figure according to PRISMA statement by the request of the editor. In the
original figure, there were 397 studies identified by the key words. We then excluded 390 by screening titles and abstracts, and limitation to RCTs. Now instead, we searched database using the key words and limited the results to RCTs in the first step. The number of studies was reduced to 63 after this first step. We believe the new figure is more consistent with the PRISMA statement and the confusing terms are removed.

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

Response: We added these information in our article: location in Table 1, and population/inclusion/exclusion criteria in the “Characteristics of included studies” paragraph as the following:

“All three trials recruited smokers who were aged 18 and over, not breastfeeding or pregnant, and had no current psychiatric or other serious illness. The inclusion and exclusion criteria were well described in two studies (Koegelenberg 2014, Ramon 2014) [9,11], requiring that the enrolled patients have no recent experience of other cessation medication or successful abstinence. The other study (Hajek 2013) provided relatively simple criteria: volunteers seeking treatment with no contraindications could be enrolled [10]. The mean age of participants was similar among all studies. One study (Koegelenberg 2014) included more female subjects than males [9]. There were 38.3% males in this study vs 66.7% and 57.8% in the other two studies respectively. The Fagerström Test for Nicotine Dependence (FTND) score was higher in one study (Ramon 2014) because it included smokers who smoked 20 or more cigarettes per day
[11], whereas the other two studies included participants with lower daily cigarettes consumption. Treatment interventions differed among these studies. One study (Koegelenberg 2014) administered trial patch two weeks before the TQD, while the other two studies started patch use on the TQD. Two studies used a 15mg/16 hours patch, while the other (Ramon 2014) used a 21mg/24 hours patch. On the other hand, the use of varenicline was similar among the studies. All started at 0.5mg per day one week before TQD, with increase to 2 mg/day on TQD, and continued for 12 weeks. One study (Koegelenberg 2014) tapered the dose of varenicline on the 13th week. All studies provided concurrent behavioral counseling during the treatment phase.”

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

Response: Thank you. We rephrased it according to your advice.

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

Response: Thank you. We rephrased it according to your advice.

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
(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).

**Response:** Thank you for mentioning these points. For (a), we used those data because the author cited it in the paragraph and used it to calculate NNT. However, we found those were not intention-to-treat data. We used intention-to-treat analysis in the other two studies. Therefore, we re-calculated our meta-analysis and updated figure 2 and 3 using intention-to-treat analysis. We also updated all OR, 95% CI and abstinence rates in the manuscript.

For (b), we understand your reverse variance analysis, however, we used Mantel-Haenszel Odds Ratio which is different from reversed-variance analysis. Mantel-Haenszel Odds Ratio is the default method in RevMan. We are sorry that we are unable to show detailed difference between these two methods, however, we are sure that you can get the same results using RevMan.

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

**Response:** Thank you for this suggestion. Heterogeneity is a critical problem that needed to be
assessed and handled carefully. It is also important to remind readers that heterogeneity must be
taken into account when interpreting the results. However, we still would like Table 2 to be
simple enough for readers to quickly grasp its clinical importance. After all, the aim of
meta-analyses is to produce conclusive and useful information from various studies.

Heterogeneity was inevitable, but was not the goal we’re looking for. At least for physicians
who are not so familiar with statistics, Table 2 is more comprehensible in its original form.

12. 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.

Response: Thank you very much, especially for providing some statistical reviews for us.