Author's response to reviews

Title: Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial.

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Author's response to reviews: see over
Dear Dr. D’Souza,

Re: MS: 8294137759031505 - Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial

We would like to thank both reviewers for their positive comments. Below are the details of the revisions requested by Dr. Fagerstrom.

INTRO, second para. Authors say that “the two medications appear alike”. Seems to me that they are only thinking about the agonist effects but varenicline also has an antagonistic effect that deserves mentioning here.

We now added: ‘In terms of observable effects on smokers, the two medications appear alike although varenicline has antagonist as well as agonist effects.’ The antagonist effects of varenicline are also mentioned in the following para.

Third para. ”Nicotine from NRT acts on all nAChRs…” I would rather say that nicotine from NRT is not specific to alpha4 beta2 or authors should provide a reference where it comes clear that NRT acts on all nACHRs.

We have adjusted the statement and it now reads: ‘Nicotine from NRT acts on nAChRs in a similar manner to nicotine from tobacco smoke, but delivery from NRT is much slower’. 

RESULTS, second para 15. It seems as the weight increase was contrary to what could be expected, more increase with active patch. Although not significant when the outlier was taken out I think it could be of interest if the authors could comment that finding a bit.

We now interpret this finding by expanding the Discussion of the ‘mechanism’ of the finding as follows: ‘One possible interpretation of the lack of synergy between the two medications is that NRT and varenicline achieve their effects via similar target mechanisms, which overlap to a large or even full extent. Varenicline may act on a more limited range of nicotinic receptors than nicotine itself, but these seem to include those involved crucially in the rewarding effects of smoking. By blocking such receptors, varenicline may be limiting any potentially beneficial effects of NRT as
well. E.g. nicotine patches normally alleviate weight gain in continuous abstainers (23) but they had no such effect here.

Table 1. In the top of the table is written for Placebo patch (N=53-59) and for Nicotine patch (56-58). It is not clear to me what is meant with 53-59 and 56-58. Did the number of patients that had given data to the variables below vary between those numbers? Please clarify.

The N-range is marked by an asterisk and the legend under the table explains that *-Ns vary due to missing data.

Further down on Cig consumption the standard deviation was 10.5 for Placebo patch but much bigger 26.3 for Nicotine patch. Was there some extreme outlyer?

Thank you for spotting this, there were actually two outliers. With the first one, weekly rather than daily consumption was entered, and the other had 10 misread by the coder as 70. The Table was corrected and coding and calculations re-checked.

Thank you for considering the revised manuscript.

Yours sincerely

[Signature]

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