PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between duration of use of pharmacotherapy and smoking cessation: Findings from a national survey
AUTHORS	Shaikh, Raees; Siahpush, Mohammad; McCarthy, Molly; Sikora, Asia; Tibbits, Melissa; Singh, Gopal

VERSION 1 - REVIEW

REVIEWER	Lindsay Stead University of Oxford UK
REVIEW RETURNED	06-Aug-2014

GENERAL COMMENTS	I do not think the authors have given sufficient weight to the major problem of reverse causation. They note; ' Moreover, there is a possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] .... Thus, individuals who use pharmacotherapies and relapse a short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse. ' In my view this is going to be the major reason for the pattern of results, especially for NRT where smokers have traditionally been discouraged against continuing to use NRT following relapse. Whilst I agree with their statement ' Smokers who intend to quit should be encouraged to use pharmacotherapy and adhere to their recommended duration of use.' unfortunately I don't think the results can be used as evidence to support it. The results could be rewritten to highlight the issue more clearly but given the limitations of the data for addressing the question it is unclear whether this is worthwhile.

REVIEWER	Paul Harrell Moffitt Cancer Center United States
REVIEW RETURNED	21-Oct-2014

GENERAL COMMENTS	General Comments This is a manuscript using a nationally representative dataset from the United States to compare rates of smoking cessation between groups of smokers based on characteristics of NRT and medication use. After adjusting for covariates, the researchers found significant differences based on duration of pharmacotherapy use. Compared to those who used prescription medications for 5 weeks or more, those who used prescription medications for shorter periods of time, used NRT for less than 5 weeks, used only behavioral help, or

	attempted to quit unassisted were all less likely to have quit. This manuscript contributes to the existing literature by addressing important issues regarding duration of usage. It provides helpful comparisons with prior literature and potential explanations of discrepant findings, which are very useful. However, some of the statements by the authors do not necessarily follow from the results and need to be modified. Major Comments 1. It is not clear what type of analyses are reported in Table 1 on page 9. Are these chi-square analyses? This needs to be clarified. 2. The authors often use omnibus tests and then use these results to make statements regarding comparisons between groups that do not necessarily follow. In some cases, post-hoc tests would be needed to make the statements suggested. For example, on page 10, lines 42-46, the authors state that "Number of cigarettes smoked per day had a curvilinear relationship with cessation such that those who smoked 0-9 cigarettes and those who smoked 20+ cigarettes per day had a higher cessation rate than others ($P < 0.001$)." This apparently is based on an omnibus test (chi-square?) that is reporting on a 5-category variable ("Cigarettes per day"). The p-value reported demonstrates that one of these 5 categories is significantly different than another one, but we do not know which one(s) or the associated p-values of comparisons without conducting additional tests. This again occurs in statements below (46-49) and above (35-42). a. On page 11, Table 2, the authors provide more helpful information with individual Odds Ratios. However, here as well, a p-value is only reported for the overall comparison. It would be helpful to provide p-values for each Odds Ratio. b. The way the analysis is currently set up, the statement at the bottom of page 11 is not justified. "Those who used…NRT for 5+ weeks had higher cessation rates….than others." We only can see that those used NRT for 5+ weeks did not differ from those who used prescription medications for 5+ weeks. 3. The abstract concludes that "Encouraging smokers who intend to quit to use pharmacotherapy and to adhere to treatment duration can help improve chances of a successful cessation." This statement is overly strong given the cross-sectional data. This should be weakened, perhaps by beginning the statement with "Results suggest….". Minor Comments 1. Buproprion and varenicline should generally not be capitalized. 2. The issue of recall bias should be mentioned. Borland, R., Partos, T. R., & Cummings, K. M. (2012). Systematic biases in cross-sectional community studies may underestimate the effectiveness of stop-smoking medications. Nicotine & Tobacco Research, 14(12), 1483-1487. 3. On page 6, it is not clear how long those considered "quit" have quit. From the abstract, it appears they have quit for less than a year. If that is true, please clarify on page 6 as well. 4. On page 6, line 37-38 it is not clear if the last quit attempt from NRT needed to be in the past year. 5. On page 8, please explain how former smokers were asked about daily consumption. This is an important question that often comes up in this type of research. In table 1, it appears that those who smoked

	30+ cigarettes were more likely to have quit than those who had not, but I suspect this is due to retrospective bias in how the questions are asked. 6. It is unclear why the overall p-value on Table 2 for Method of quit attempt is significant, but none of the Odds Ratios are significant. Perhaps using another referent than Prescription Only would clarify this. I thank the authors for their efforts and the editor for the opportunity to review.

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER #1

COMMENT: I do not think the authors have given sufficient weight to the major problem of reverse causation. They note; ' Moreover, there is a possibility of reverse causation such that relapse would determine duration of pharmacotherapy use rather than vice versa.[35] .... Thus, individuals who use pharmacotherapies and relapse a short while after a quit attempt may stop using these aids. In such cases, an unsuccessful quit attempt would cause a short duration of pharmacotherapy use instead of the reverse. ' In my view this is going to be the major reason for the pattern of results, especially for NRT where smokers have traditionally been discouraged against continuing to use NRT following relapse. Whilst I agree with their statement ' Smokers who intend to quit should be encouraged to use pharmacotherapy and adhere to their recommended duration of use.' unfortunately I don't think the results can be used as evidence to support it. The results could be rewritten to highlight the issue more clearly but given the limitations of the data for addressing the question it is unclear whether this is worthwhile.

RESPONSE: We agree with the reviewer. We have given more weight to the issue of reverse causation by mentioning it as a first weakness of the study. Moreover, we have indicated that “there is a strong possibility of reverse causation” (emphasis added). We have devoted a whole paragraph to the issue of causality and have expounded the possibility of reverses causation. Please, see fourth full paragraph in “Discussion” section.

Furthermore, in the Results section we have been careful not to use the language of causation; instead we have used phrases such as “the association of method of quit attempt with the probability of smoking cessation” and “the association of duration of pharmacotherapy use with the probability of smoking cessation.” Similarly, in summarizing the results in the Discussion section, we have described the findings in terms of associations without reference to causality or direction of causation. (see, Discussion, first paragraph).

Finally, following the reviewer’s comment that the last sentence in the Discussion is not supported by the results, we have removed that sentence.

RESPONSE TO REVIEWER #2

COMMENT: 1. It is not clear what type of analyses are reported in Table 1 on page 9. Are these chi-square analyses? This needs to be clarified.

RESPONSE: We have added a table foot note indicating that chi-square analysis was employed.

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COMMENT: 2. The authors often use omnibus tests and then use these results to make statements regarding comparisons between groups that do not necessarily follow. In some cases, post-hoc tests would be needed to make the statements suggested. For example, on page 10, lines 42-46, the authors state that "Number of cigarettes smoked per day had a curvilinear relationship with cessation such that those who smoked 0-9 cigarettes and those who smoked 20+ cigarettes per day had a higher cessation rate than others ($P < 0.001$)." This apparently is based on an omnibus test (chi-square?) that is reporting on a 5-category variable ("Cigarettes per day"). The p-value reported demonstrates that one of these 5 categories is significantly different than another one, but we do not know which one(s) or the associated p-values of comparisons without conducting additional tests. This again occurs in statements below (46-49) and above (35-42).
a. On page 11, Table 2, the authors provide more helpful information with individual Odds Ratios. However, here as well, a p-value is only reported for the overall comparison. It would be helpful to provide p-values for each Odds Ratio.
b. The way the analysis is currently set up, the statement at the bottom of page 11 is not justified. "Those who used…NRT for 5+ weeks had higher cessation rates….than others." We only can see that those used NRT for 5+ weeks did not differ from those who used prescription medications for 5+ weeks.

RESPONSE: We have omitted all references to comparisons in describing the bivariate results shown in Table 1. We have noted in a table footnote that the p-values are based on chi-square tests.

We have provided p-values for all odds ratios in Table 2.

The statement "Those who used prescription medication for 5+ weeks or NRT for 5+ weeks had higher cessation rates, 28.8% and 27.8% respectively, than others" is based on the results shown in Figure 2. The figures 28.8% and 27.8% pertain to cessation rates expressed in absolute percentages; they do not indicate risk ratios or odds ratios. We have reworded this statement to clarify that fact.

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COMMENT: 3. The abstract concludes that "Encouraging smokers who intend to quit to use pharmacotherapy and to adhere to treatment duration can help improve chances of a successful cessation." This statement is overly strong given the cross-sectional data. This should be weakened, perhaps by beginning the statement with "Results suggest….".

RESPONSE: We thank the reviewer for this suggestion and have made the suggested change.

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COMMENT: Buproprion and varenicline should generally not be capitalized.

RESPONSE: We have corrected this error.

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COMMENT: 2. The issue of recall bias should be mentioned. Borland, R., Partos, T. R., & Cummings, K. M. (2012). Systematic biases in cross-sectional community studies may underestimate the effectiveness of stop-smoking medications. Nicotine & Tobacco Research, 14(12), 1483-1487.

RESPONSE: We have mentioned this issue and have cited Borland et al 2012. Please, see the fifth full paragraph in "Discussion" section..

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COMMENT: 3. On page 6, it is not clear how long those considered “quit” have quit. From the abstract, it appears they have quit for less than a year. If that is true, please clarify on page 6 as well.

RESPONSE: We have clarified this in the first sentence in the “Measurement” section.

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COMMENT: 4. On page 6, line 37-38 it is not clear if the last quit attempt from NRT needed to be in the past year.

RESPONSE: We have added the phrase “in the past” year to the sentence.

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COMMENT: 5. On page 8, please explain how former smokers were asked about daily consumption. This is an important question that often comes up in this type of research. In table 1, it appears that those who smoked 30+ cigarettes were more likely to have quit than those who had not, but I suspect this is due to retrospective bias in how the questions are asked.

RESOPONSE: The question about daily smoking was: “Around this time 12 months ago were you smoking everyday …?” We have included this question in the first sentence in the “Measurement” section.

The observed pattern of relationship between number of cigarettes per day and quitting is consistent with previous literature. Because this was tangential to the paper, we did not expound it. The relationship is said to be partly because of most extremely dependent smokers who try to quit are particularly motivated to make a robust effort at quitting. Highly dependent smokers are least likely to try to quit, so those who did make an attempt may be usually motivated (Shiffman et al 2008).

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COMMENT: 6. It is unclear why the overall p-value on Table 2 for Method of quit attempt is significant, but none of the Odds Ratios are significant. Perhaps using another referent than Prescription Only would clarify this.

RESPONSE: The pattern that the reviewer refers to is not uncommon and as the reviewer indicates it is because of the choice of the reference category. Changing the reference category only changes the presentation of the results and the conclusions remain unchanged. We did not change the reference category as we feel the order in which the categories of method of quit attempt is presented in the table is more suitable and is consistent with the lower panel of Table 2.

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COMMENT: I thank the authors for their efforts and the editor for the opportunity to review.

RESPONSE: We thank this reviewer for the very useful comments and their kindness.

VERSION 2 – REVIEW

REVIEWER	Paul Harrell Moffitt Cancer Center, USA
REVIEW RETURNED	11-Dec-2014

GENERAL COMMENTS	I thank the authors for their responses. However, I have a few remaining concerns. My concerns that the abstract conclusions were overly broad are strengthened by reading the first reviewer's comment. Although I thank the authors for adjusting the 2nd sentence, I feel the first sentence of the abstract conclusion remains too strong. I suggest limiting the conclusion to stating that those who used pharmacotherapy for at least five weeks were more likely to have achieved smoking cessation. Although results are certainly consistent with general advice to adhere to pharmacotherapy treatment duration, these data are not sufficient in themselves for demonstrating that pharmacotherapies can be effective in the general population if used for at least 5 weeks. The overall p-values on Table 2 remain confusing. I am not sure the relevance of the finding that method of quit attempt is significant, but none of the groups are significant in comparison to the referent. I would suggest eliminating these overall p-values as I rarely see them when Odds Ratios are presented and their implications are not clear in this paper. The primary outcome measure should be specified in more detail in the abstract. How is successful smoking cessation defined?

VERSION 2 – AUTHOR RESPONSE

RESPONSE TO REVIEWER #2

COMMENT: Please state any competing interests or state 'None declared': None declared

RESPONSE: We had a "Conflict of Interest Statement" added at the end of the manuscript and we have now also added a statement to this segment saying "No competing interest to declare".
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COMMENT: 2. I thank the authors for their responses. However, I have a few remaining concerns. My concerns that the abstract conclusions were overly broad are strengthened by reading the first reviewer's comment. Although I thank the authors for adjusting the 2nd sentence, I feel the first sentence of the abstract conclusion remains too strong. I suggest limiting the conclusion to stating that those who used pharmacotherapy for at least five weeks were more likely to have achieved smoking cessation. Although results are certainly consistent with general advice to adhere to pharmacotherapy treatment duration, these data are not sufficient in themselves for demonstrating that pharmacotherapies can be effective in the general population if used for at least 5 weeks.

RESPONSE: We have now rephrased the first sentence of conclusion section according to your suggestion.
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COMMENT: 3. The overall p-values on Table 2 remain confusing. I am not sure the relevance of the finding that method of quit attempt is significant, but none of the groups are significant in comparison to the referent. I would suggest eliminating these overall p-values as I rarely see them when Odds Ratios are presented and their implications are not clear in this paper.

RESPONSE: We have deleted the category wise p-values from table 2 only leaving the overall covariate p-values to indicate the presence or absence of their significant association with the outcome.
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COMMENT: The primary outcome measure should be specified in more detail in the abstract. How is successful smoking cessation defined?

RESPONSE: We have added the description in abstract to clarify how the primary outcome measure was defined.
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