BMJ - Decision on Manuscript ID BMJ.2015.024776

Body: 27-Feb-2015

Dear Dr. Fazel

Manuscript ID BMJ.2015.024776 entitled "Varenicline and the risk of psychiatric disorders, suicidal behaviour, criminal offending, and transport accidents and offences: population-based cohort study"

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest in the report below from the manuscript meeting: we are provisionally offering acceptance but will make the final decision when we see the revised version.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Please note too that we would like to publish your paper along with a study on a similar research question, so we would be very happy if you would return your revision within the proposed timeframe.

https://mc.manuscriptcentral.com/bmj?URL_MASK=ee00dafdf6364d7792e04bfe52fd9ea5

Yours sincerely

dr. Wim Weber
European editor, BMJ
wweber@bmj.com,

Decision: provisional acceptance

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available below.

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

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If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes , and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

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Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: Elizabeth Loder (Chair), Gary Collins (Statistics advisor), Rebecca Burch, José Merino, Emma Parish, Georg Röggla, Wim Weber.

Decision: provisional acceptance

Detailed comments from the meeting: we had nothing to add to the comments by the external reviewers.

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

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c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at http://resources.bmj.com/bmj/authors/bmj-pico

d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis”

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

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Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed

groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)

For a systematic review and/or meta-analysis:
point estimates and confidence intervals for the main results

one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
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for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
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was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
This is a well conducted, well written, important, and timely report of a within-subject analysis in a large cohort of people to detect whether use of varenicline is associated with suicide, crime, motor vehicle accidents, or new psychiatric 'disorders'.

The primary substantive critique is that, while the increased risk for affective disorders, etc, in those with nicotine dependence is controlled for in this study with

the within-subject design, because anxiety and depressed mood are prominent features of the nicotine withdrawal syndrome, a control group with both nicotine dependence and likely nicotine withdrawal (those attempting to quit smoking) would be important to include to clarify the likely contribution of varenicline use, per se, to this risk of affective 'disorders'. Those who used bupropion or NRT could be included as controls in an analysis expanded to include those treatments to address the concern that the finding is due to smoking cessation and not due to use of varenicline per se. This addition would vastly improve our ability to interpret the results in terms of the contribution of varenicline to the outcome.

Secondly, in the abstract and discussion, it should be emphasized that increased risk for affective 'disorders' was observed ONLY for those with pre-existing psychiatric illness. Again, it would be critical to interpretation of the results to understand whether this is also the case with other pharmacotherapeutic cessation aids.

More minor comments:
Introduction, second paragraph, please add 2 citations, first authors, Hong and Shim, as placebo-controlled studies of varenicline in those with serious psychiatric illness that found no evidence of worsening of psychiatric symptoms in those assigned to varenicline compared to placebo. The FDA prescribing information now cites summary data from RCT's not published and could be cited as a URL. The Kishi and Iwata meta-analysis is badly flawed in that it incorrectly summarizes the evidence for efficacy of varenicline for smoking cessation in schizophrenia and does not formally assess safety of varenicline in this population, as such it is not helpful here as a reference.

In Results
In the first paragraph, please clarify whether the 5.6% crime rate was the increase during treatment over the incidence before treatment.

Use of the term 'disorders' is not optimal as operationalized for this study, as this may have been a transient phenomenon.

Summary:
For the between subject hazard models, positive controls with bupropion and NRT are critical for interpretation. The between subject models do not control for the increased risks of these outcomes in persons with nicotine dependence or the increased risks for psychiatric symptoms due to the smoking cessation process /nicotine withdrawal.

Additional Questions:
Please enter your name: Eden Evins

Job Title: Cox Family Associate Professor of Psychiatry

Institution: Harvard Medical School

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

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Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: Pfizer

Reviewer: 2

Recommendation:

Comments:
This report is very strong overall. The stepwise description of the results is clear. Addressing several points could strengthen the piece.

The final sentence of paragraph 2 suggests there is no literature clinicians can use to weigh the risks and benefits of varenicline use in individuals with psychiatric illness – when really there are the cited trials (32-35). These studies are RCTs that have demonstrated safe use of varenicline in individuals with bipolar disorder, major depression, and schizophrenia. I appreciate that the authors are saying that RCTs may not pick up rare events, though so far RCTs are reassuring.

The analysis testing for confounding by pre-existing psychiatric disorders showed that only individuals with pre-existing psychiatric illnesses had increased HR of mood and anxiety disorders. This is an interesting point and brings up the question of what proportion of individuals with pre-existing psychiatric disorders were getting treatment for what are typically chronic problems such as recurrent major depression or anxiety disorders. It also brings up the question of whether anxiety or depression symptom recurrence is occurring here, particularly if the majority of individuals were not receiving treatment or were receiving insufficient treatment (which is unknown but a possibility). It is not stated in the Discussion that the incidence for new psychiatric disorders was only significant in the group with pre-existing psychiatric disorders. Could the authors address these points in the Discussion and contrast this finding with the RCTs (ie citation 34 by Anthenelli, et al. which showed no increase in depression symptoms among individuals with major depression treated with varenicline, though over 70% of trial participants were receiving concurrent treatment with an antidepressant medication). There may be room in the Discussion to include reflecting on these points if the authors condensed the recap of the results (ie the first paragraph of the Discussion).

Additional Questions:
Please enter your name: Joseph Cerimele

Job Title: Physician

Institution: University of Washington School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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