PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Are 'dual users' who smoke and use e-cigarettes interested in using varenicline to stop smoking altogether, and can they benefit from it? A cohort study of UK vapers.
AUTHORS	Hajek, Peter; Peerbux, Sarrah; Phillips-Waller, Anna; Smith, Charlotte; Pittaccio, Kate; Przulj, Dunja;

VERSION 1 - REVIEW

REVIEWER	Lion Shahab University College London
REVIEW RETURNED	08-Nov-2018

GENERAL COMMENTS	This is an interesting and worthwhile addition to the literature. I recommend publication but would suggest a number of relatively minor changes to the manuscript, detailed below. 1) Please specify hypotheses explicitly or make clearer in your introduction that this is an exploratory study. 2) Sample size: This number arrived at (200) seems somewhat arbitrary. I would suggest considering why this sample would be sufficient to provide meaningful estimates, by referring to estimation of bounds such as 95%CI that would be sufficiently narrow. For instance, given that a key aim is to assess interest in this population to use varenicline, you could argue that a meaningful result would be to determine whether at least 10% of the population would be interested. In order to obtain a reliable estimate with 95%CI being within 5% of the estimate, you would require a sample size of at least 200 participants (10% with 95%CI 15.0-6.5). 3) Your data analysis section is too sparse. How were results for main outcome analysed (chi-square analysis does not provide RR or associated CI). 4) As mention in 2) – given the main aim is to determine interest, I would strongly suggest to provide 95%CI for your estimates described in the first paragraph on page 8. 5) I appreciate the complication in validating abstinence from vaping in continued smokers and vice versa (although one would assume that anabasine levels in EC only users would be lower than in smokers). However, in table 2 it would be preferable to provide the validated abstinence rates for those stopping both EC and cigarettes, rather than unvalidated results. 6) In table 4, it is unclear why you restrict the analysis to 3 months follow-up only. You would have more power doing a MANOVA or similar using all three timepoints (baseline, 3 and 6 months follow-up) to asses enjoyment of smoking and vaping among those who did not stop using either.

	7) Table 5 is difficult to follow. I would suggest presenting changes in cotinine levels across time by group as a line graph. 8) Given that a major limitation of this work is that participants were not randomised, I would suggest including a sensitivity analysis of the main outcomes (ie. abstinence) which controls for all baseline characteristics (e.g. using GEE). This should provide more reliable estimates. 9) Throughout the manuscript, referencing is relatively sparse. If you make declarative statements, please provide appropriate references (e.g. page 13, third paragraph, last sentence). 10) Another key limitation should be added: namely, that this was not a randomly selected sample but a self-selected sample so generalisability is unclear. You could strengthen your conclusion by comparing characteristics of your sample to the wider population of dual users (e.g. by referring to published APS or STS data).

REVIEWER	Zheng-Xiong Xi National Institute on Drug Abuse, USA
REVIEW RETURNED	09-Nov-2018

GENERAL COMMENTS	This study examined the potential utility of varenicline in dual users who smoke cigarettes and use e-cigarettes and demonstrates significant interest in using varenicline to quite smoke and e-cigarettes. I have a few major concerns below. 1) As the authors claimed that most of the related studies are regarding the use and efficacy of varenicline in quitting cigarette smoking, little is known about the effects of varenicline in quitting e-cigarettes. From this point, the related findings appear to be novel. However, these findings are not surprising, since it is well known that varenicline is an alpha4beta2 nicotinic receptor partial agonist and functionally antagonizes the pharmacological action of nicotine provided by E-cigarettes. As the authors stated, smokers use e-cigarettes mainly as an alternative medication to quite smoking. It is unclear whether e-cigarette use and abuse is a problem. Otherwise, the significance of the findings in this study is problematic. 2) It is unclear which varenicline dose(s) were used in this study. It looks like that only one varenicline dose was used. Were the effects dose-dependent? 3) It is an open-labeled study without a placebo control. In addition, the weekly support calls may also contribute to the "beneficial effects of varenicline". 4) All the data were presented in Tables, which appears confusing and hard to follow. The authors may consider to use bar or linear figures to show the observed effects over time.

REVIEWER	Nicholas Zwar University of New South Wales, Australia
REVIEW RETURNED	05-Dec-2018

GENERAL COMMENTS	This is a novel and timely study exploring an interesting question in tobacco control in the era of e-cigarettes. It is known that many people who use e-cigarettes are dual users, that is they also continue to smoke tobacco. As the authors state there has been

	little research on whether these people are interested in stop smoking medicines and whether they could benefit from them. The findings of the study are of considerable interest as they suggest that considerable numbers of dual users are interested and may benefit from stopping smoking, stopping vaping or both. The study should be a trigger for further work in this area. The design is a cohort of dual users recruited via social media and not a trial design. In general the authors do a good job of describing the limitations of the study but this could be improved as follows: - mention in abstract that recruitment was via social media - in limitations comment on the possible impact of the method of recruitment - e.g. may be a younger group than dual users as a whole, may be higher socioeconomic status, may be more health literate. Also given that social media can reach a very large number of people those who responded to the invitation may be much more interested in behaviour change and using smoking cessation medicines than dual users in general. - the loss to follow-up was substantial and this should be noted as a limitation. Another comment is that the authors assume that people are dual users primarily because they an to reduce their use of combusted tobacco. Is this a safe assumption? It may be that people dual use because it expands their opportunities for use of nicotine, saves money or some other motivation.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Thank you for the positive comments.

1. Please specify hypotheses explicitly or make clearer in your introduction that this is an exploratory study.

We now say in the introduction (page 3) that this was an exploratory study. (The project was set up to assess what % of dual users are interested in varenicline and how v. affects smoking and vaping – i.e. the study asked questions for which answers are not known, rather than testing specific hypotheses).

2. Sample size: This number arrived at (200) seems somewhat arbitrary. I would suggest considering why this sample would be sufficient to provide meaningful estimates, by referring to estimation of bounds such as 95%CI that would be sufficiently narrow. For instance, given that a key aim is to assess interest in this population to use varenicline, you could argue that a meaningful result would be to determine whether at least 10% of the population would be interested. In order to obtain a reliable estimate with 95%CI being within 5% of the estimate, you would require a sample size of at least 200 participants (10% with 95%CI 15.0-6.5).

We now specify in the sample size section on page 5-6 that … ‘For instance, if 10% of the respondents would be interested in using varenicline, this sample size would provide 95% probability of the true population proportion falling within the range of 5.8% to 14.1%.’

3. Your data analysis section is too sparse. How were results for main outcome analysed (chi-square analysis does not provide RR or associated CI).

We have now added this, see page 6.

4. Given the main aim is to determine interest, I would strongly suggest to provide

95%CI for your estimates described in the first paragraph on page 8.

This has now been done (see page 6).

5. I appreciate the complication in validating abstinence from vaping in continued smokers and vice versa (although one would assume that anabasine levels in EC only users would be lower than in smokers). However, in table 2 it would be preferable to provide the validated abstinence rates for those stopping both EC and cigarettes, rather than unvalidated results.

This has now been done.

6. In table 4, it is unclear why you restrict the analysis to 3 months follow-up only. You would have more power doing a MANOVA or similar using all three time points (baseline, 3 and 6 months follow up) to assess enjoyment of smoking and vaping among those who did not stop using either.

This was because we were interested in any effects of varenicline on enjoyment of nicotine, and the 3-M follow is proximal to the drug use period.

7. Table 5 is difficult to follow. I would suggest presenting changes in cotinine levels across time by group as a line graph.

We now present this as graphs (see Figures 2 and 3).

8. Given that a major limitation of this work is that participants were not randomised, I would suggest including a sensitivity analysis of the main outcomes (ie. abstinence) which controls for all baseline characteristics (e.g. using GEE). This should provide more reliable estimates.

We discuss the higher dependence and higher nicotine intake in varenicline users, but also point out that they could have been more motivated to quit; and that they received telephone support. As we do not have any measure of the key motivational variable, and cannot control for support as this was given to all varenicline users, controlling just for dependence and nicotine intake (the only baseline variables likely to be related to outcome) would just further magnify the effect, but would not help in its interpretation. An RCT is needed to clarify the issues, as noted in the Discussion.

9. Throughout the manuscript, referencing is relatively sparse. If you make declarative statements, please provide appropriate references (e.g. page 13, third paragraph, last sentence).

Reference now added.

10. Another key limitation should be added: namely, that this was not a randomly selected sample but a self-selected sample so generalisability is unclear. You could strengthen your conclusion by comparing characteristics of your sample to the wider population of dual users (e.g. by referring to published APS or STS data).

This is now acknowledged in the discussion of study limitations on page 12 ‘Finally, this was not a random sample. Recruitment via social media may have attracted a sample with characteristics that are not representative of the wider population of dual users and the generalisability of the results is thus unclear.’

We are also now more circumspect in the conclusion and say that there ‘seems to be’ a high level of interest.

Reviewer: 2

1) As the authors claimed that most of the related studies are regarding the use and efficacy of varenicline in quitting cigarette smoking, little is known about the effects of varenicline in quitting e-cigarettes. From this point, the related findings appear to be novel. However, these findings are not surprising, since it is well known that varenicline is an alpha4beta2 nicotinic receptor partial agonist and functionally antagonizes the pharmacological action of nicotine provided by E-cigarettes. As the authors stated, smokers use e-cigarettes mainly as an alternative medication to quit smoking. It is unclear whether e-cigarette use and abuse is a problem. Otherwise, the significance of the findings in this study is problematic.

We agree that the finding that varenicline affects e-cigarette use is novel, but not surprising. A confirmation of the effect is nevertheless potentially useful. The finding that dual users are interested in using smoking cessation pharmacotherapy however seems to us to be both novel and surprising.

2) It is unclear which varenicline dose(s) were used in this study. It looks like that only one varenicline dose was used. Were the effects dose-dependent?

Varenicline was up-titrated as per labelling. This is now made clearer in the Methods section on page 4. ‘Participant up-titrated varenicline use from ½ mg per day for three days through ½ mg twice per day for the rest of the first week and to 1mg twice a day for the rest of the course, as per product labelling’.

3) It is an open-labeled study without a placebo control. In addition, the weekly support calls may also contribute to the "beneficial effects of varenicline".

These are valid points, acknowledged in the Discussion.

4) All the data were presented in Tables, which appears confusing and hard to follow. The authors may consider to use bar or linear figures to show the observed effects over time.

We now present data on cotinine levels as Figures (see Figures 2 and 3).

Reviewer 3

Thank you for positive comments.

Mention in abstract that recruitment was via social media

We have now updated this.

In limitations comment on the possible impact of the method of recruitment - e.g. may be a younger group than dual users as a whole, may be higher socioeconomic status, may be more health literate. Also given that social media can reach a very large number of people those who responded to the invitation may be much more interested in behaviour change and using smoking cessation medicines than dual users in general.

We now state in the discussion of study limitations on page 12: ‘Finally, this was not a random sample. Recruitment via social media may have attracted a sample with characteristics that are not representative of the wider population of dual users and the generalisability of the results is thus unclear’.

The loss to follow-up was substantial and this should be noted as a limitation.

We now include this on page 12: ‘Loss to follow-up represents another study limitation’. However, we do not think this affected the results. For the uptake of varenicline, those not responding were included as not wanting varenicline. Drop-outs were also included in vaping/smoking cessation data as non-abstainers.

Another comment is that the authors assume that people are dual users primarily because they want to reduce their use of combusted tobacco. Is this a safe assumption? It may be that people dual use because it expands their opportunities for use of nicotine, saves money or some other motivation.

We agree that some dual users may well have other motives, but data we were able to locate and that we cite suggest that most smokers use e-cigarettes to reduce or stop smoking.

VERSION 2 – REVIEW

REVIEWER	Lion Shahab University College London
REVIEW RETURNED	23-Jan-2019

GENERAL COMMENTS	All comments have been addressed satisfactorily.

REVIEWER	Nicholas Zwar Bond University, Australia
REVIEW RETURNED	29-Jan-2019

GENERAL COMMENTS	Authors have responded comprehensively to comments from reviewers and editor.