PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of nicotine mouth spray on urges to smoke, a randomised clinical trial
AUTHORS	Hansson, Anna ; Hajek, Peter; Perfekt, Roland; Kraiczi, Holger

VERSION 1 - REVIEW

REVIEWER	Lindsay Stead Cochrane Tobacco Addiction Review Group Dept of Primary Care Health Sciences, University of Oxford No Competing interests
REVIEW RETURNED	24-Jul-2012

THE STUDY	Technically since these patients weren't trying to stop smoking they weren't necessarily representative but has no effect on validity of study. I can't comment definitively on statistical methods but they appear well enough described to be sound!
RESULTS & CONCLUSIONS	The main limitation which is lack of ability to blind is addressed.
GENERAL COMMENTS	I have 2 minor comments/suggestions. There seemed to be no mention in the text of the data from the second half of the figure, which suggests that while craving declines more rapidly with the mouth spray it also increases again sooner. This is probably unsurprising if it is absorbed and subject to metabolism more quickly but could merit a comment. Also the reported incidence of hiccups and nausea seems high and it would be helpful if it was possible to compare this to the levels reported for the clinical trial.

REVIEWER	Prof Kerenza Hood South East Wales Trials Unit Institute of Translation, Innovation, Methodology and Engagement School of Medicine Cardiff University UK I have no competing interests
REVIEW RETURNED	11-Aug-2012

THE STUDY	It is a real shame that this study was not done as a double dummy design given the self reported nature of the outcome. This is acknowledged by the authors and I think it is a well done study that contributes towards the evidence base, but does not give a definitive answer for htat reason. One thing I think could potentially be done more of is explore what the mechanism of action might be if it was a perceived benefit. From my brief glance at the previous study by this

	group, the increase in nicotine in the blood is maximised as 10 mins post administration. I wonder if it might be worth them doing a sensitivity analysis excluding the changes seen at the first minute, which may be more likely to be attributable to experience of administration than the actual nicotine (although I acknowldege that I am not an expert in the speed of this). In the methods section I would like to see details of how potential carry over effects are assessed. I also note that the acheived sample size for complete cases is identical to the calculation. Did they continue until they achieved that size, in which case can this be stated in the methods.
RESULTS & CONCLUSIONS	I think more discussion and sensitivity analysis needs to be done (see above), but the results look credible.
REPORTING & ETHICS	The CONSORT checklist is fine, but I would like to see a flowchart in the paper.
GENERAL COMMENTS	It would be interesting to know how long it usually takes a lozenge to dissolve (and hence release the dose of nicotine).

VERSION 1 – AUTHOR RESPONSE

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I have 2 minor comments/suggestions. There seemed to be no mention in the text of the data from the second half of the figure, which suggests that while craving declines more rapidly with the mouth spray it also increases again sooner. This is probably unsurprising if it is absorbed and subject to metabolism more quickly but could merit a comment.
Response: A comment has been added to the Discussion section (page 18): Although focus of this study was on the immediate effects of the study treatments on urges to smoke, measurements were made up to 2 hours after administration. It appears from Figure 1 as if not only the start but also the decline of relief from urges to smoke occurred faster with mouth spray than with lozenges. This observation is paralleled by not only a faster absorption of nicotine from mouth spray than lozenge but also a faster decline of plasma nicotine concentrations5.

Also the reported incidence of hiccups and nausea seems high and it would be helpful if it was possible to compare this to the levels reported for the clinical trial.
Response: It is difficult to compare the adverse events reported in this single-dose study with those reported in the clinical trial with 12 weeks treatment. It can, however, be concluded that the most commonly reported adverse events in the current trial were common also in the clinical study. A comment has been added to the Discussion section (pages 20-21): In a recent clinical trial comparing the nicotine mouth spray with placebo7, hiccups, throat irritation, nausea, dyspepsia, mouth irritation, salivary hypersecretion, burning sensation in mouth, and constipation were the more common in the nicotine group, but the ratings of acceptability of the nicotine mouth spray were good and only 9.1% of subjects on active spray withdrew due to adverse events, compared to 7.5 % on placebo.

It is a real shame that this study was not done as a double dummy design given the self reported nature of the outcome. This is acknowledged by the authors and I think it is a well done study that

contributes towards the evidence base, but does not give a definitive answer for that reason. One thing I think could potentially be done more of is explore what the mechanism of action might be if it was a perceived benefit. From my brief glance at the previous study by this group, the increase in nicotine in the blood is maximised as 10 mins post administration. I wonder if it might be worth them doing a sensitivity analysis excluding the changes seen at the first minute, which may be more likely to be attributable to experience of administration than the actual nicotine (although I acknowledge that I am not an expert in the speed of this).
Response: The study focuses on effects on craving but was not restricted to pharmacological effects. E.g. it is not unlikely that sensory effects contribute relatively more immediately after administration while the relative impact of absorbed nicotine increases over time. A sensitivity analysis excluding the changes seen at one minute would compare treatments from one minute onward. But in view of an already observed difference at one minute, any such comparison would suffer from a systematic difference in 'baseline values' with the spray data using an on average lower degree of craving as a starting point. Therefore, no additional analysis has been performed.

In the methods section I would like to see details of how potential carry over effects are assessed.
Response: The possible effects of carry-over were assumed small relative to main effects of treatments and in the primary analysis no attempt was therefore made to test for this or any other treatment-by-period interaction. Post hoc we have performed a sensitivity analysis by restricting the data for treatment comparisons to values recorded during the very first study session. In this subset of data no carry-over effects can exist. The outcome of this post hoc analysis consistently showed p-values less than 0.001 for each comparison in analogy with reported values shown in Table 1, page 15. Estimated treatment differences were similar but somewhat more pronounced compared to the full data analysis presented in Table 1. (Due to the exclusion of approximately two thirds of the data values, the calculated confidence intervals were however correspondingly wider). Thus we conclude that the reported treatment differences in Table 1 are not exaggerated due to carry-over. An addition has been made to the Methods section (page 12).

I also note that the achieved sample size for complete cases is identical to the calculation. Did they continue until they achieved that size, in which case can this be stated in the methods.
Response: The following addition has been made to the Methods section (page 11): "To allow for drop-outs, recruitment continued until 200 subjects were included in the study." Also, a flow diagram to describe the progress of subjects through the phases of the study has been added (Figure 1).

I think more discussion and sensitivity analysis needs to be done (see above), but the results look credible.

The CONSORT checklist is fine, but I would like to see a flowchart in the paper.
Response: A flowchart has been added (Figure 1).

It would be interesting to know how long it usually takes a lozenge to dissolve (and hence release the dose of nicotine).
Response: This was not measured in the current trial. However, in the pharmacokinetic study on mouth spray (reference 5) the lozenge was used as reference product and dissolved in on average 24 minutes upon per label use which is consistent with information provided by GSK in their SmPC. The following addition has been made to the Methods section (page 9): "A lozenge typically dissolves in 20-30 minutes."