CORRESPONDENCE

Comment on: Effect of a nicotine-free inhalator as part of a smoking cessation programme

To the Editors:

The study by CAPONNETTO *et al.* [1] in the November 2011 issue of the *European Respiratory Journal* addresses the behavioural part of smoking. The purpose of this comment is to offer a constructive review of the research and suggestions for further research.

In this study at a smokers' clinic, 120 smokers were given pharmacological treatment at their choice but were also randomised to receive a cigarette-like nicotine-free inhalator loaded with a sponge soaked in naturally extracted herbal aroma oil.

The smoking cessation results showed no main effect of this inhalator but quite a pronounced effect of the inhalator in a group with a supposedly high degree of behaviour dependence to smoking. The behaviour dependence was measured according to the Glover–Nilsson Smoking Behavioral Questionnaire (GN-SBQ) scale. This questionnaire asks how important the behavioural part of smoking is [2].

In the intention-to-treat analysis at 24-week follow-up, 28% and 33% were not smoking in the reference (no inhalator) and inhalator groups, respectively. In the group of subjects with high behaviour dependence (>22 points on the GN-SBQ), the corresponding cessation rates were 19% and 67% ($p<0.007$). This finding is surprisingly strong, given everything we know about predictors for smoking cessation outcome, particularly since the GN-SBQ so far has not shown any acceptable validity. Only one study is cited in support of the scale [2], which does not prove validity.

Based upon the findings in this study, several questions emerge that may benefit future replications of this study. First, how was the cut-off of 22 points on the GN-SBQ chosen? Was it an *ad hoc* decision? Secondly, how were the pharmacological treatments distributed between the groups? Was there an interaction of pharmacological treatment and inhalator use? Thirdly, treatments usually have their best effect early on in the trials. In this trial, the effect of the inhalator was stronger at week 24 than at week 4. Did subjects use more of the inhalator after week 4? How did the use pattern look over time? Fourthly, it is one thing to accept that the inhalator could be effective for those with high behaviour dependence but somewhat difficult to understand that it should negatively influence outcome in the low behaviour dependence group. One would think that all daily smokers, smoking a mean of 25 cigarettes·day⁻¹ over a mean period of 29 yrs, would be behaviourally dependent. How did the use pattern of the inhalator vary between the two treatment groups? Finally, it would be of more general interest to know the correlation

between the GN-SBQ and the Fagerström Test for Nicotine Dependence to clarify whether the two types of dependencies are independent of each other or correlated. I would assume that a smoker highly dependent on nicotine would also tend to be more behaviourally dependent.

In conclusion, smokers differ in dependence profiles and the problems they face when stopping smoking. Better diagnosis of the smokers, which this study aims for, could ultimately lead to tailoring treatments and boosting efficacy [3]. This first study was small and needs to be replicated with larger samples and by other investigators. Until then, we have to be cautious, but some further analysis of the data from this study as suggested here could at least shed some more light on the matter.

K. Fagerström

Fagerström Consulting, Kågeröd, Sweden.

Correspondence: K. Fagerström, Fagerström Consulting, Jordkull 3670, 26878 Kågeröd, Sweden. E-mail: karl.fagerstrom@swipnet.se

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To the Editors:

In their recent publication, CAPONNETTO *et al.* [1] described the effect of randomised nicotine-free inhalator use during a smoking cessation intervention with 24 weeks of follow-up. Interestingly, the effect differed in direction according to the degree of nicotine dependency assessed by the Glover–Nilsson Smoking Behavioral Questionnaire, with a reduced smoking quit rate among low-rate dependency persons and an increased quit rate among high-rate dependency persons.

The authors in their methodology described to be using the Fagerström Test for Nicotine Dependence (FTND), and it would be of interest also to know whether estimates with FTND as dependency parameter gave a similar result. Also, it would be of interest to know the actual duration of nicotine-free inhalator use in each of the two groups (median and range), and whether the concordance with the smoking cessation intervention (bupropion and high-dose nicotine patch) differed in the two groups, if these data are available.

C.N. Meyer

Respiratory Disease Unit, Dept of Internal Medicine, Roskilde Hospital, Roskilde, Denmark.

Correspondence: C.N. Meyer, Respiratory Disease Unit, Dept of Internal Medicine, Roskilde Hospital, Kogevej 7-13, 4000 Roskilde, Denmark. E-mail: cnm@regionsjaelland.dk

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From the authors:

We are pleased that our recent work published in the *European Respiratory Journal* regarding the positive role of a nicotine-free inhalator (Paipo; Echos Srl, Milan, Italy) used in the context of smoking cessation interventions [1] has attracted so much interest. In particular, we are grateful to K. Fagerström and C.N. Meyer for raising a number of stimulating and relevant points. A pronounced effect on quit rates was observed with Paipo in smokers with a supposedly high degree of behaviour dependence to smoking (*i.e.* in those for whom handling and manipulation of their cigarettes played an important part in the ritual of smoking). This was measured by the Glover–Nilsson Smoking Behavioral Questionnaire (GN-SBQ), which determines the importance of the behaviour component in smoking dependence [2].

Based on the current knowledge of predictors of smoking cessation [3], the pronounced effect on quit rates observed with Paipo in the participants with high behaviour dependence to smoking was surprising. There may be several explanations for this. Using a different cut-off point on the GN-SBQ scale might have affected results, but we have followed the recommendations of the GN-SBQ developers and used the canonical cut-off point of 22 for the analyses [2]. Alternatively, our findings reflect the fact that aspects of tobacco dependence that are behavioural in nature are very little studied and that characterisation of behavioural sub-phenotypes in smokers may be a far stronger and more relevant determinant of smoking cessation outcomes [4]. We agree with K. Fagerström that future research has to address in

depth the behavioural component of tobacco dependence in smoking cessation studies.

A second area of concern was the possibility of unbalanced distribution of pharmacological treatment between the two study groups. By study design, all participants in both groups were prescribed high-dose nicotine patch plus bupropion 300 mg per day. However, it cannot be established with confidence whether the level of adherence to medical treatment was similar between groups.

It was incorrectly pointed out that "...the effect of the inhalator was stronger at week 24 than at week 4". Overall in the Paipo study group, quit rates decreased from 38.3% at week 4 to 33.3% at week 24. The use pattern of Paipo varied widely, particularly in relation to their level of behaviour dependence to smoking. In most cases with high GN-SBQ, use of Paipo was perceived as extremely helpful and maintained constant throughout the study with a median usage of 6 weeks. Quite a few of these patients continued using Paipo *ad libitum* even after termination of the study. However, the majority of cases with low GN-SBQ lost confidence in the utility of Paipo very quickly and discontinued its use.

The notion that participants with low behaviour dependence levels quickly lost confidence in the utility of Paipo may also explain why the product negatively influenced quit rates in this specific sub-group. The Paipo might not have helped with coping with some of the psychological/behavioural aspects of tobacco dependence in the low GN-SBQ group, thus failing to meet the expectations of these smokers undergoing the smoking cessation programme. This failure experience by itself would constitute an additional stressor, and its associated decrease in self-efficacy should produce increased negative affect [5]. This is likely to be the cause of an additional sense of failure and more stress. Smokers in these stressful situations react by adopting the best coping strategy known to them, *i.e.* lighting up a cigarette. Therefore, in smokers with low GN-SBQ scores, the Paipo could cause a paradoxical effect, the product triggering relapse in order to compensate for the additional frustration/stress. Besides, the purpose of the study may convey to participants the message that there is an easy remedy for tobacco addiction (*i.e.* "the nicotine free inhalator may help you stay quit during your attempt"), thus generating false expectations in the smokers' mind. This, unintentionally, would produce a boomerang effect that undermines motivation to continue to abstain from smoking in some participants (particularly those with low GN-SBQ scores), who would then quickly relapse. This interpretation is speculative and warrants specifically designed study, but, if confirmed, smokers with low GN-SBQ scores should not be given the device. In addition, we have shown that success rates in smokers with low GN-SBQ scores appear to be markedly dependent on their initial level of motivation (OR 12.7). Although motivation levels (assessed at baseline by Mondor test) were evenly distributed between the Paipo and reference study groups, as well as between low GN-SBQ and high GN-SBQ subgroups, and considering that smoking cessation is not an event but a process, the predictor variable "level of motivation" recorded at baseline may not be very representative of the dynamic psychological and physical changes occurring in the smokers struggling to quit. Dynamic changes in motivation levels may occur in both