

**EXPERT
OPINION****Comment and reply on:
A randomized crossover trial
investigating the ease of use and
preference of two dry powder
inhalers in patients with asthma
of chronic obstructive pulmonary
disease**

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I read with great interest the article by Job van der Palen *et al.* [1]. The article describes the comparison of a new single-dose dry powder inhaler, Elpenhaler (EH) (Elpen Pharmaceutical Co., Inc., Greece) versus the established dry powder inhaler, Accuhaler/Diskus (DK) (GlaxoSmithKline, UK) in patients with chronic obstructive pulmonary disease (COPD) and asthma. The basic conclusion of the authors is as follows: 'With DK fewer errors were made, more patients preferred DK over EH and patients were more satisfied with DK'. It is the purpose of this letter to demonstrate that this conclusion is misleading since it is based on serious oversights of the design of the study.

First, and most importantly, at the time that the study was conducted, EH was not marketed in the Netherlands. It is assumed that 'instructions of usage' were translated from English to Dutch (Methods section). It seems that the translation was not accurate as the translation of a unique characteristic and one of the major advantages of the EH device (i.e., visual verification of dose uptake) was omitted. EH allows the patient to visually check after inhalation whether the powder has been inhaled or not. Consequently, the Elpenhaler checklist quoted in Table 1 of the article should have included prior to the last 'Close inhaler' step as an additional step for the correct use of the device: *After inhalation, check whether all the inhalation powder has been inhaled.*

Second, in Section 2.2 entitled, 'Patients', one reads 'Patients were 40 years ... were naive to DK and EH for at least 1 year'. It cannot be questioned that the patients were naive to EH; however, it can be questioned whether patients were really naive to DK, since – as stated in Table 2 – disease history ranged between 3 and 13 years. In addition, 72.6% of patients suffered from COPD and fluticasone-salmeterol combination is the drug of choice for this disease. Up to now, besides DK, there is no other combination of those two active ingredients in clinical practice. Doctors and nurses were also naive to EH and not naive to DK; the instructions of medical doctors and nurses to the patients for the correct use of EH relied on the content of the insert and not on their real-life clinical experience with the EH device, compared to DK.

The methodology of the study can be questioned since current medical practice for asthma and COPD patients requires the training of the patients before regular use of the inhalation device. The study showed that 110 DK patients (97.3%) and 100 EH patients (88.5%) correctly used the devices after one single instruction (Table 3). The above finding strengthens the position of current medical practice

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concerning the necessity of proper patient training before the use of any inhalation device.

Overall, the main disagreement concerning the article of Job van Palen *et al.* [1] is that the design of their study incorporates a ‘bias’ in favor of DK.

Bibliography

1. van der Palen J, van der Valk P, Goosens M, et al. A randomized cross-over trial investigating the ease of use and preference of two dry powder inhalers in patients with asthma of chronic obstructive pulmonary disease. *Expert Opin Drug Deliv* 2013;10(9):1171–8

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Author's response

We would like to respond to this letter that according to the writer has the purpose ‘to demonstrate that this [our] conclusion is misleading since it is based on serious oversights of the design of the study’. The author is referring to our basic conclusion: ‘With DK fewer errors were made, more patients preferred DK over EH and patients were more satisfied with DK’.

The author is correct in assuming that the ‘instructions of usage’ were translated from English to Dutch. We would like to thank the writer of this letter for pointing out our error in not including ‘visual verification of dose uptake’ in our error checklist. What is not clear from the manuscript is the exact content of the instruction sheet. This was translated from English and did include the statement on ‘visual verification of dose uptake’. Therefore, the patients knew that they could verify whether or not the dose had been successfully inhaled.

Below, I will summarize the consequences of our omission of adding ‘visual verification of dose uptake’.

Our primary outcome was the percentage of patients making one or more critical error after reading the insert, while the secondary outcomes were: the percentage of patients making one or more critical errors after the first instruction by the trainer; the number of instructions needed to demonstrate a perfect inhalation technique; overall patient satisfaction; and inhaler preference. If one would consider visual verification of dose uptake as a critical

Declaration of interest

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error, then the percentage of patients making a critical error with the Elpenhaler could only go up. In the unlikely event that no patient would make this error, the difference in critical error rate would remain 17% for Diskus versus 35% for Elpenhaler ($p = 0.001$). Any extra patient making an error with the item ‘visual verification of dose uptake’ would further enlarge the difference in favor of the Diskus. The same is true for critical error rate following instruction by the trainer and the number of instructions needed.

The effect of adding the visual inspection item to the checklist will not have influenced our third secondary outcome, which is overall patient satisfaction, because this was included in the instruction sheet. The same probably holds true for our last secondary outcome, which is inhaler preference, in which the observed difference is very large, with 73.2% of patients preferring Diskus versus 26.8% preferring Elpenhaler ($p < 0.001$).

Furthermore, the author of the letter states: ‘...however, it can be questioned whether patients were really naive to DK, since—as stated in Table 2—disease history ranged between 3 and 13 years. In addition, 72.6% of patients suffered from COPD and fluticasone–salmeterol combination is the drug of choice for this disease’. On this topic we can be clear. All the included patients were truly naive to the Diskus. Contrary to the belief of the author, there are many patients that do not use the Diskus for the fluticasone–salmeterol combination in the Diskus.

In a further comment, the role of familiarity of the instructors with the Diskus and not the Elpenhaler was

addressed: ‘Doctors and nurses were also naive to EH and not naive to DK; the instructions of medical doctors and nurses to the patients for the correct use of EH relied on the content of the insert and not on their real-life clinical experience with the EH device, compared to DK’. This is undoubtedly true, but would not have made any difference to our primary outcome: ‘the percentage of patients making one or more critical errors after reading the insert’.

Finally, the author questions the methodology of the study, ‘... since current medical practice for asthma and COPD patients requires the training of the patients before regular use of the inhalation device’. We do not agree that the methodology of the study is incorrect. One can only criticize us for the choice of primary outcome parameter. We chose assessment of critical

errors after reading the instructions only – not because we feel this is how it should be done in practice but because we often encounter referred patients who have never been instructed. Our paper shows that this is an unacceptable practice, but more so for some inhalers than for others.

Declaration of interest

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