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New developments in inhaler devices within pharmaceutical companies: A systematic review of the impact on clinical outcomes and patient preferences

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ABSTRACT

Background: Pharmaceutical companies offer an increasing number of inhaler devices, whether or not together with new substances, for maintenance treatment of patients with COPD or asthma. However, well-designed studies to support these developments are scarce.
Objectives: The aim of this research was to evaluate how far new developments of inhaler devices are scientifically supported and translate into improvements of patient preferences and/or clinical outcomes.
Methods: A systematic literature review was performed to retrieve randomised controlled trials in patients with COPD or asthma that studied the in-company evolution of inhaler devices. Results were tabulated and discussed.
Results: A total of 30 studies were found comparing Respimat® vs. HandiHaler®, Diskus®(Accuhaler®) vs. Diskhaler®(Rotadisk®) or pMDI, Ellipta® vs. Diskus®(Accuhaler®), Nexthaler® vs. pMDI, or Breezhaler® vs. Aerolizer®. These studies show that developments of inhaler devices may improve patient satisfaction but do not lead to demonstrable improvements in clinical efficacy. Current changes of devices are most commonly parallelled by changes in administration frequency towards once daily treatment. The only well-documented effect was found for the Respimat® Soft Mist™ Inhaler, which realises a more than 3-fold lowering of the once-daily tiotropium dose through increased performance of the inhaler device. There are however, no data on clinical efficacy or safety comparing the two devices at the same dosage.
Conclusions: Future developments of inhaler devices should all require well-designed studies to demonstrate patient benefit.

1. Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are common obstructive airways diseases that have a major impact on morbidity and mortality of patients worldwide [1,2]. Inhalation medication is nowadays the mainstay of pharmacological treatment [3]. The major classes of maintenance medication include long-acting bronchodilators, either β_2-agonists (LABA) or muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS) [1,2]; these drugs are used either alone or in various combinations.

Comparative efficacy and safety of class-representative molecules and their combinations have extensively been studied in

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randomised controlled trials, as reported in reviews [4,5]. However, a closer look at these studies shows that little attention is given to the role of the inhaler devices that are used to administer these molecules. The inhaler devices are often 'assumed' to be clinically equivalent, are not taken into consideration as potentially confounding variables in treatment comparisons, or device names are not reported at all. Several studies exist that have looked specifically at inhaler devices, using softer endpoints, such as patient satisfaction and preferences. It is difficult to perform such studies in a randomized and blinded way, and there is no common validated method to assess these parameters. The risk for bias towards the newer devices should not be neglected. Moreover, using the preferred inhaler device is not necessarily associated with less administration errors, according to a cross-sectional assessment of inhaler technique and patient preferences in 301 adults with asthma or COPD [6].

In recent years, various innovations have improved the efficiency and performance of the inhaler devices. Together with the technological progress, the importance of patient ability to use the device properly and the educational role of the physician herein, received much attention [7]. On top of this, new active substances have been developed, such as substances characterized by a longer duration of action [8]. Therefore, the evolution of inhalation treatment developed within pharmaceutical companies active in the field, often - but not always - associates a new device with a new active substance.

The objective of the present study was to review how the evolution of handheld devices with/without new active substances - within pharmaceutical companies - impacts on patient preferences and/or clinical outcomes in COPD and asthma patients. For this purpose, we performed a systematic review of the medical literature with focus on the latest developments of inhalation treatments within pharmaceutical companies. Evolutions of chlorofluorocarbon to hydrofluoroalkane propelled pressurized metered dose inhalers - being merely based on environmental concern over the use of chlorofluorocarbon propellants - were out of our scope.

2. Material and methods

The research question was how the evolution of handheld devices with/without new active substances - within pharmaceutical companies – was supported by randomised controlled trials and which type of improvement was reported. We looked at in-company developments, thereby excluding comparisons of devices of different companies. Only the latest developments were evaluated; past evolutions of pressurized metered-dose inhalers (pMDI) to dry powder inhalers (DPI) or chlorofluorocarbon-to hydrofluoroalkane-propelled pMDIs were not considered in this review.

A systematic review of the PubMed database was performed in August 2014 by a panel of specialists in respiratory medicine from Belgium and Luxembourg. Our search criteria included randomised controlled trials in patients with COPD or asthma, using the following keywords:

a) Respimat® and HandiHaler®, inhaler devices delivering tiotropium bromide (Boehringer Ingelheim);
b) Diskus® (or Accuhaler®) and Diskhaler® (or Rotadisk®), inhaler devices delivering fluticasone propionate or salmeterol xinafoate (GlaxoSmithKline);
c) Diskus® (or Accuhaler®) and pMDI, inhaler devices delivering salbutamol, salmeterol or fluticasone propionate (GlaxoSmithKline);
d) Diskus® (or Accuhaler®) and Ellipta®, inhalers used to deliver salmeterol xinafoate and fluticasone propionate or vilanterol trifenatate and fluticasone furoate respectively (GlaxoSmithKline);
e) Nexthaler® and pMDI, inhaler devices delivering beclomethasone dipropionate and formoterol fumarate (Chiesi Farmaceutici);
f) Aerolizer® (Foradil® inhaler) and Breezhaler®, inhaler devices delivering formoterol fumarate or indacaterol maleate respectively (Novartis).

The meeting abstracts of the American Thoracic Society (ATS 2014), the European Respiratory Society (ERS 2013), the American College of Chest Physicians (ACCP 2013) and the ClinicalTrials.gov database were consulted for additional studies. The panel of experts in pulmonary medicine was contacted for further information and insights to complete the search results. The reference lists of the retrieved publications were also examined for additional studies.

All titles and abstracts were hand searched for relevancy. Trials that met the inclusion criteria were appraised by one reviewer; results were verified by a second reviewer, with any discrepancies being resolved through agreement with a third reviewer.

The primary endpoints (efficacy, safety or patient preferences) were tabulated.

3. Results

Four pharmaceutical companies reported on switching their current inhaler device to a novel inhaler system with or without new active substances (Table 1). The predefined systematic database search resulted in a total of 174 published articles, 48 meeting abstracts and 26 clinical trials having results. Via hand-search of titles and abstracts for relevancy to the research questions, we retrieved 30 randomised controlled trials that studied at least two devices with/without new active substances within the same company in patients with asthma or COPD (Table 1).

4. Respimat® vs. HandiHaler®

The LAMA tiotropium is available either for administration via the dry powder inhaler HandiHaler® or via the novel Respimat® Soft Mist™ Inhaler. We retrieved five randomised controlled trials, all performed in COPD patients (Table 2). Parameters were similar between treatment arms [same molecule: tiotropium; same dosing frequency: once daily (OD)], except for the inhaler device and the

Table 1
Number of randomised controlled trials.

Manufacturer	Inhaler device	COPD	Asthma	Reference
Boehringer Ingelheim	Respimat® vs. HandiHaler®	5		[9–13]
GlaxoSmithKline	Diskus® vs. Diskhaler®		7	[14–20]
	Diskus® vs. pMDI		3	[21–23]
	Ellipta® vs. Diskus®	3	5	[24–31]
Chiesi	Nexthaler® vs. pMDI		1	[32]
Novartis	Breezhaler® vs. Aerolizer®	5	1	[33–38]

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