BRN Reviews REVIEW

Demystifying Inhaler Use in Chronic Obstructive Airways Disease

Matteo Bonini, MD, PhD, Omar S. Usmani, MD, PhD

National Heart and Lung Institute (NHLI), Imperial College London & Royal Brompton Hospital, UK

ABSTRACT

Chronic obstructive airways diseases afflict millions of people worldwide, being responsible for significant morbidity and mortality. Despite progresses in the understanding of the pathophysiological mechanisms and advances in the therapeutic interventions, neither asthma nor chronic obstructive pulmonary disease (COPD) can be cured as yet, although both diseases can be optimally controlled. Inhaler therapy plays a crucial role in achieving this and allows personalised treatment strategies to patients. However, satisfactory adherence and correct technique in the use of inhaler devices can be particularly challenging. The present review aims to present updated and evidence-based literature findings to shed light on the role and relevance of inhaler devices in chronic obstructive airways diseases and provide readers with clear information and advice about the use of inhalers in the variety of options available, to recognise the crucial inhaler errors and gain an insight with respect to recent innovation addressing the unmet needs in the field. **(BRN Rev. 2018;4(4):304-18)**

Corresponding author: Matteo Bonini, m.bonini@imperial.ac.uk

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Correspondence to:
Matteo Bonini, MD, PhD
Imperial College London & Royal Brompton Hospital
National Heart and Lung Institute (NHLI)
Airways Disease Section
Dovehouse Street
London SW3 6LY, UK
E-mail: m.bonini@imperial.ac.uk

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INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are widespread chronic obstructive airways diseases that afflict a vast number of individuals, being responsible for significant morbidity and mortality[1]. Approximately 300 million people worldwide suffer from asthma, with an additional 100 million subjects estimated to be affected by 2025[2]. Likewise, around 15 million people have a physician-diagnosis of COPD in the United States[3]. Of relevance, COPD has been ranked among the top leading causes of death in the world[4] and, together with asthma, dramatically affects patients' quality of life[5]. These overwhelming figures translate into significant healthcare costs and a considerable socio-economic burden[6].

Despite progresses in the understanding of the pathophysiological mechanisms and advances in the development of new therapeutic strategies, neither asthma nor COPD can be cured, as yet. However, both diseases can be optimally controlled, and the role of inhaler devices is crucial in achieving this by personalising treatment strategies to patients[7]. Inhalation therapy is the mainstay of treatment in patients with chronic respiratory conditions, where bronchodilators (i.e. beta$_2$ agonists and anti-muscarinic agents) and anti-inflammatory drugs (i.e. glucocorticoids) are recommended by international strategy documents, at any stage of disease severity[8,9]. Inhaled treatment has indeed several advantages over systemic therapy allowing the delivery of active molecules directly to the target site of action, whilst minimising side effects and adverse events[10]. Furthermore, compared with oral administration, a lower quantity of drug dose is needed to achieve the therapeutic effect and the onset of action is more rapid through the inhaled route[11].

However, the use of inhaler devices in asthma and COPD can be challenging. Studies demonstrate significant misuse in handling, as well as non-adherence towards recommended treatment regimens, which are key issues in the therapeutic efficacy and health economics of inhaled pharmacological interventions[12,13]. The features contributing to adherence to inhaled medications are complex, but a crucial element is patients having the correct inhaler technique to ensure adequate drug delivery, otherwise, erroneously, they may feel the device is ineffective[14]. A recent systematic review conducted to identify main errors in inhaler use and their impact on health outcomes and resources, showed wide heterogeneity in the term "critical error"; where 299 definitions were identified in the scientific literature[15]. The authors also observed an important association between inhaler misuse and worsened health outcomes, highlighting the importance of achieving optimal inhaler technique and the need for a consensus on the definition of critical and non-critical errors. Furthermore, with over 200 available drug-inhaler device combinations (Fig. 1), significant confusion may arise for healthcare professionals, and matching the patient's characteristics, needs and preferences to the most appropriate inhaler device becomes crucial. Indeed, most prescribers in pulmonary medicine focus on the class medication and specific drug molecule, but the importance of pertinent inhaler selection is becoming increasingly recognised in achieving disease control[16].

This present review aims to present updated and evidence-based literature findings to shed light on the role and relevance of inhaler devices

Figure 1. Examples of available inhaler devices.

in chronic airways diseases, provide readers with clear information and advice about the use of inhalers, in the variety of options available in day-to-day practice, to recognise the key inhaler errors and gain an insight with respect to recent innovation addressing the unmet needs in the field.

THE RANGE OF CURRENTLY AVAILABLE INHALER DEVICES

Aerosols, either solutions containing the medication or solid drug particles suspended in gas or dry powder, can be delivered through pressurised metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), soft-mist inhalers (SMIs) or nebulisers (Table 1). In recent years, several technological innovations in device engineering and formulation science have significantly improved the performance of all existing inhaler categories, with the new generation of devices having pulmonary deposition fractions of 40–50% the nominal dose[17].

Pressurised metered-dose inhalers are compact devices that require no agent preparation and offer high dose-to-dose reproducibility. The first commercial pMDI was developed in the late 1950's by Riker Laboratories as a portable, multi-dose delivery device for bronchodilator drugs[7]. The subsequent generation of pMDIs consisted of aluminium canisters, containing a pressurised suspension of micronised drug particles dispersed in chlorofluorocarbon (CFC) propellants. In suspension formulations, active drugs are not soluble in the propellant and remain in a state of solid powder, making

Table 1. Main characteristics of available inhaler devices

Devices	Advantages	Disadvantages	Instructions for patients
Pressurised metered-dose inhalers (pMDIs)	Portable; not dependent on inspiratory flow; reproducible dosing; wide variety of drugs available; no contamination risk; low cost	Ozone-depleting properties (chlorofluorocarbon- [CFC] driven); better perform with spacers (CFC-driven); need to be shaken prior use (CFC-driven); hand-breath coordination required; high oropharyngeal deposition; cold freon effect	Shake well (CFC-driven); prime inhaler the first time; hold inhaler upright; exhale fully; seal lips around the mouthpiece; press the dose release button while inhaling through the mouth slowly and deeply; hold breath for 5-6 s; exhale slowly
Dry powder inhalers (DPIs)	Portable; no hand-breath coordination required; fast drug delivery; dose counter or individually packaged dose; no spacer required	Inspiratory flow dependent; dexterity in dose loading and activation needed for single-dose devices; poor dose reproducibility; additional devices for rescue medications required	Load and activate the dose; exhale fully; seal lips around the mouthpiece; inhale quickly and deeply for 2-3 s; hold breath for 5-6 s; exhale slowly
Nebulisers	Easy to use; propellant free; no hand-breath coordination required; not dependent on inspiratory flow; slow velocity aerosol; high patient's adherence	Not portable; power source needed; long drug delivery time; potential higher risk of respiratory infections; device cleaning and maintenance frequently needed	Carefully load medication dose following instructions; ensure face mask is well in place; inhale through the mouth slowly and deeply; clean device after each use
Soft-mist inhalers (SMIs)	Auto lock when cartridge is empty; propellant free; slow velocity aerosol; long plume duration; no hand-breath coordination required; high fine particle fraction and smaller drug particle size; no spacer required	Dose loading into device required; strength and dexterity needed	Insert cartridge before use; write down expire date on cartridge; prime inhaler the first time; hold inhaler upright with cap closed; turn base until it clicks; exhale fully; seal lips around the mouthpiece; inhale through the mouth slowly and deeply; press the dose release button and continue to inhale as long as possible; hold breath for 5-6 s; exhale slowly

it necessary to shake the device before use to ensure uniform distribution of the particles and a constant emitted dose at each actuation. However, following the Montreal Protocol Declaration banning the use of CFC propellants, due to their ozone-depleting properties, pharmaceutical companies started to develop hydrofluoroalkane (HFA) propellants[18]. In HFA-solution pMDIs, the drug is uniformly distributed in the canister and does not require any shaking prior to use. Currently, pMDIs represent the most commonly prescribed inhalers for drug delivery to the airways thanks to the relatively low cost and the wide variety of medications available with this technology[19]. Extreme temperatures and/or high altitudes may affect the drug in the pMDI. Therefore, the patient must always check the inhaler label for storage instructions. Importantly, the correct use of pMDIs requires a slow and deep inhalation and some degree of coordination is required between inhalation and device actuation[20]. To avoid these issues, the combined use of a pMDI with a spacer may be helpful, especially in children and elderly patients who may have problems with dexterity. There is less need however for spacers with the newer generation of HFA-solution pMDIs, as these devices have slower velocity aerosols with smaller size or fine drug particle fractions, and are less flow-dependent, meaning there is

consistency of dose delivery to the lungs independently from the patient inhalation flow[21]. Breath-activated (BA) pMDIs, now available for many years, have been shown to be advantageous in patients with poor coordination[22]. Breath-activated-pMDIs contain a conventional pressurised canister, with a flow triggered system driven by a spring, which releases the drug dose during inhalation, so that firing and inhaling are automatically coordinated. They can be also actuated at an inhalation flow, which is easily achievable by most patients. Recent studies have shown improved drug deposition and increased patient confidence with the use of BA-pMDI's, but the greatest limiting factor for their dissemination is represented by the restrict availability of agent molecules for these particular devices[23].

Dry powder inhalers are equally small and portable inhaler devices. The first DPI was introduced in 1971 by Bell et al.[24] to deliver therapy to COPD patients. Since then, a broad number of DPIs have entered the market, each with its own particular handling instructions and specific inhalation threshold and manoeuvre. Dry powder inhalers, particularly those of early generation, do not require coordinated activation, however they need a careful approach by the patient to dose loading and dose preparation, since an incorrectly prepared DPI will be clinically ineffective even with optimal handling and inhalation technique. Dry powder inhaler devices can also be flow-dependent leading to variability in drug delivery to the lungs in relation to the patient inhalation flow through the device[25]. In addition, most conventional DPIs are influenced by the energy in the patient inhalation for breaking apart and dispersing the dry powder contained in the device. These factors may lead to reduced levels of drug deposition (~ 20%) to the lungs at low patient inhalation flows[26], and recent data show an increased risk of readmission in patients discharged on DPIs following an acute exacerbation of COPD, where in this scenario they usually have suboptimal inspiratory flow rates[27]. Recent innovations in DPI engineering have advanced this category with a newer generation of inhalers (i.e. capsule-based and extra-fine DPIs) that are activated and achieve high levels of lung deposition (> 40%) even at low patient inhalation flows (~ 30 l/min or less)[28,29].

Nebulisers are motor-driven devices that produce a fine mist for delivery to the lungs and represent one of the earliest systems for inhalation therapy[30]. Commonly, nebulisers are distinguished into two main categories: jet nebulisers and ultrasonic nebulisers[31]. In jet nebulisers, a high-velocity air stream moves through a narrow capillary tube and carries the large droplets of liquid to baffles throughout the nebuliser, which breaks these droplets down so that they can be sufficiently small to be inhaled by the patient. On the other hand, ultrasonic nebulisers use sound waves, generated by the vibration of piezoelectric crystals at high frequency, to break down the liquid into the smaller droplets required for inhalation. Ultrasonic nebulisers are typically more expensive and less efficient than jet nebulisers, and can increase the temperature of the solution, making them unsuitable for heat-sensitive agents. Nebulisers are often used in patients who are hospitalised, with acute exacerbations or with advanced lung disease, who may be too dyspnoeic and impaired to complete a proper respiratory manoeuvre. Compared with other device categories, nebulisers may be viewed as a time-consuming and inefficient means of

delivering aerosol medication. This is particularly evident when more than one agent is prescribed for disease management, as combination products are not widely available in all countries in a nebulised format. Another common concern with nebulisers is microbial contamination, which may expose patients to the risk of respiratory tract infections[32]. However, new nebuliser systems have been developed to decrease the inefficiency, waste, and variability of nebulised drug delivery. In regard to this, vibrating mesh disk nebulisers, powered by a compressor and containing a microchip, control drug delivery to the patient and have an adaptive aerosol system to pulse the inhaled drug during the inhalation. This therefore leads to less dose wastage, positively impacting on patient's adherence[33]. A smart nebuliser system containing an electronic smart-card unit with an air compressor to accurately dose and target aerosol delivery, has also been developed lately, showing better efficacy and patients' adherence compared to standard nebulisers[34]. New handheld multi-dose nebulisers have been at last newly marketed with the potential to compete with both pMDIs and DPIs on the portable inhaler market[35].

At last, **SMIs**, equally considered to be nebulisers, are composed of propellant-free liquid solutions that are inhaled as a fine aerosol mist through a mouthpiece containing a control valve to release medication[36]. Soft mist inhalers deliver the drug solution using mechanical energy produced by a spring, generating a fine, slow-moving mist over a slightly longer period compared to other devices (1.2-1.5 s versus 0.15-0.35 s). This allows patients more time to synchronise actuation and breathing, possibly reducing the errors that occur due to poor coordination[37]. Soft mist inhalers also offer additional technological advances such as a high fine particle fraction (~ 75%) and smaller drug particle size in the respirable range[38]. These features lead to low levels of drug deposition in the oropharynx and high total lung deposition (>50%), effectively targeting the site of disease[39]. Patients using SMIs may require additional support in the assembly and proper priming procedures[40]. Like pMDIs, SMIs can also be combined with spacers, although the combination is yet to be fully evaluated.

PRINCIPAL ERRORS IN INHALER USE

Patient adherence to prescribed treatment has been shown to represent a crucial link between effective therapy and improved disease outcomes. However, several studies have revealed unsatisfactory compliance with guideline recommendations[41] and inhaler therapy use (Fig. 2)[42]. Medication underuse, overuse, and improper use are three common forms of patient non-adherence. Adherence to inhaled corticosteroids (ICS) has been reported to be an independent strong predictor of long-term asthma control[43]. Furthermore, the results of a systematic review highlighted that satisfactory treatment adherence was associated with a lower risk of severe asthma exacerbations in both adult and paediatric populations[44]. Interestingly, Sulaiman et al.[45] showed that an intervention with (bio)feedback on the features of inhaler use identified refractory asthma and enhances inhaler technique and adherence. Medication adherence is estimated to be only 10–40% in patients with COPD and decreases with time

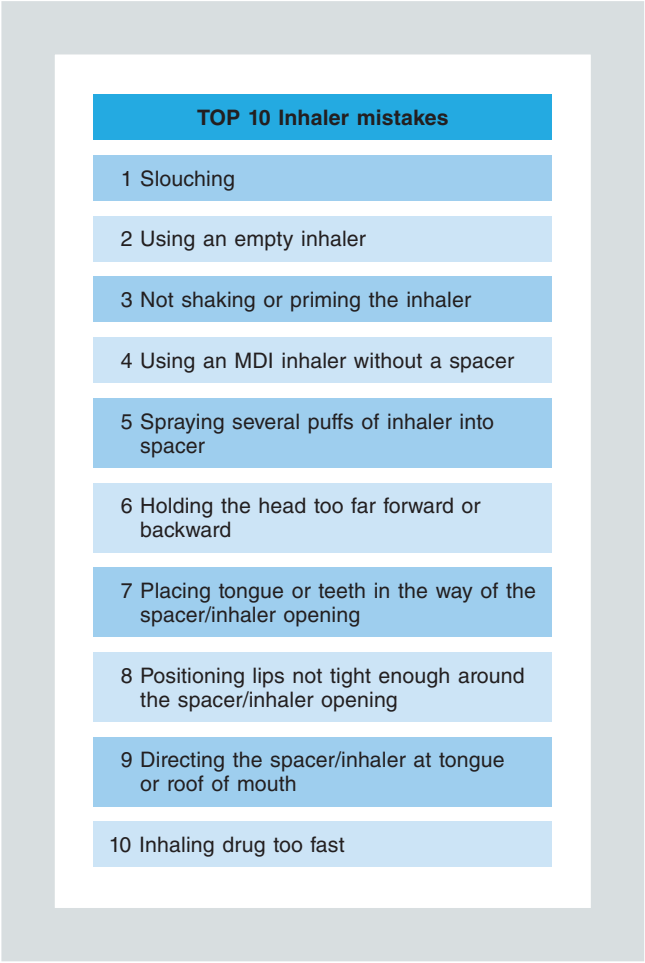

Figure 2. Top 10 inhaler mistakes. *Modified from the National Jewish Health (www.njhealth.org).*
MDI: metered-dose inhaler.

following the first prescription. Alarmingly, only 6% of the 244 severe COPD patients studied with an electronic audio-recording device (INCA), had an adherence rate greater than 80% following discharge from hospital[46]. Distinct adherence behaviours have been shown to be associated with specific clinical outcomes in COPD[47]. Low adherence results in poor symptom control, worsened quality of life and mortality rates two to three times higher than those seen in patients with good compliance[48]. Inhaler technique error is a frequent cause of non-adherence in COPD patients, commonly associated with unscheduled healthcare resource utilisation and poor symptom control.

To properly understand and quantify device-use errors, so that patient interventions can be effectively introduced and new devices designed, it is relevant to correctly define critical and non-critical errors, as well as to carefully identify the number and type of checklist steps for each specific device. A critical error is one that may impact the effectiveness of the delivered drug and thereby lead to sub-optimal disease control, whereas a non-critical error is one of the checklist steps that is not classified as critical[49].

The CRITical Inhaler mistaKes and Asthma controL (CRITIKAL) study investigated the association between specific inhaler errors and asthma outcomes, using data from the initiative Helping Asthma in Real-life Patients (iHARP) asthma review service. People with asthma receiving a fixed-dose combination treatment with inhaled glucocorticoids and long-acting β_2-agonists were categorised by the controller inhaler device they used (i.e. DPIs or pMDIs). The report included data from 3660 patients, and showed that insufficient inspiratory effort with DPI users was common (32-38%) and significantly associated with uncontrolled asthma and increased exacerbation rate. In pMDI users, actuation before inhalation (25% of patients) was associated with uncontrolled asthma[50].

A review of 21 studies addressing pMDI use revealed that the prevalence of poor inhaler technique ranged from 14% to 90% (with an average of 50%). Furthermore, the use of multiple inhaler devices in an individual patient

was shown to be associated with a higher prevalence of errors compared to the use of single devices[51].

In a cross-sectional study[52], patients with asthma were observed for serious inhaler errors by trained healthcare providers. Among 3681 asthmatics, 341 (55%) patients made ≥ 1 critical errors. Those most commonly observed were failure to exhale before inhalation, inadequate breath-hold at the end of inhalation, and inhalation not sufficiently forceful from the start. Factors significantly associated with ≥ 1 serious errors included poor asthma control in the previous four weeks, as well as asthma-related hospitalisation and no inhaler technique review during the previous year. Interestingly, females and obese subjects were the demographic categories showing worse inhaler technique.

Sanchis et al.[53] reported the most common errors observed during the various steps of a pMDI inhalation manoeuvre to be in breath holding (24-77%), shaking the inhaler (7-57%) and firing the inhaler while breathing-in slowly (10-68%), with only a 34% weightedaverage share of patients showing adequate inhaler technique. In contrast, when assessing the errors in the inhalation manoeuvre with DPIs, they found breathing-out and breath-holding to be the major issues.

A recent meta-analysis found overall and critical error rates to be particularly high across all devices, ranging from 50% to 100% and from 14% to 92%, respectively. A trend towards higher error rates was observed with devices requiring a greater number of checklist steps[54], and together with other researchers[55], have called for the need to standardised checklists and definitions for inhaler error studies to ensure consistency across the literature in order to interpret data meaningfully.

HOW TO CHOOSE THE BEST INHALER

While no single inhalation device is perfect, the wide variety of available device options supports tailored and optimised device selection based on patients' characteristics, needs and preferences[56].

The three most important factors influencing inhaled drug deposition within the airways are the patient's inhalation flow, the aerosol velocity and the drug particle size. These factors ultimately impact on the amount of drug reaching the airways and consequently on the functional and clinical response of patients[57-59]. The choice of an inhaler device in patients with chronic airways diseases should therefore take in high consideration such parameters. In example, for patients who encounter most difficultly with coordination of actuation and inhalation, a DPI may be the most suitable device. Conversely, for patients unable to generate a hard, fast breath with an adequate peak inspiratory flow rate, a pMDI or a SMI may be a better option. A pragmatic algorithm in choosing the right inhaler device for the right patient has recently been published (Fig. 3)[60], and there are standards available to check the competency of those involved in inhaler device demonstration[61].

Since different inhalers have unique requirements for their individual operation, the use of more than one device in the management of respiratory diseases can create confusion about

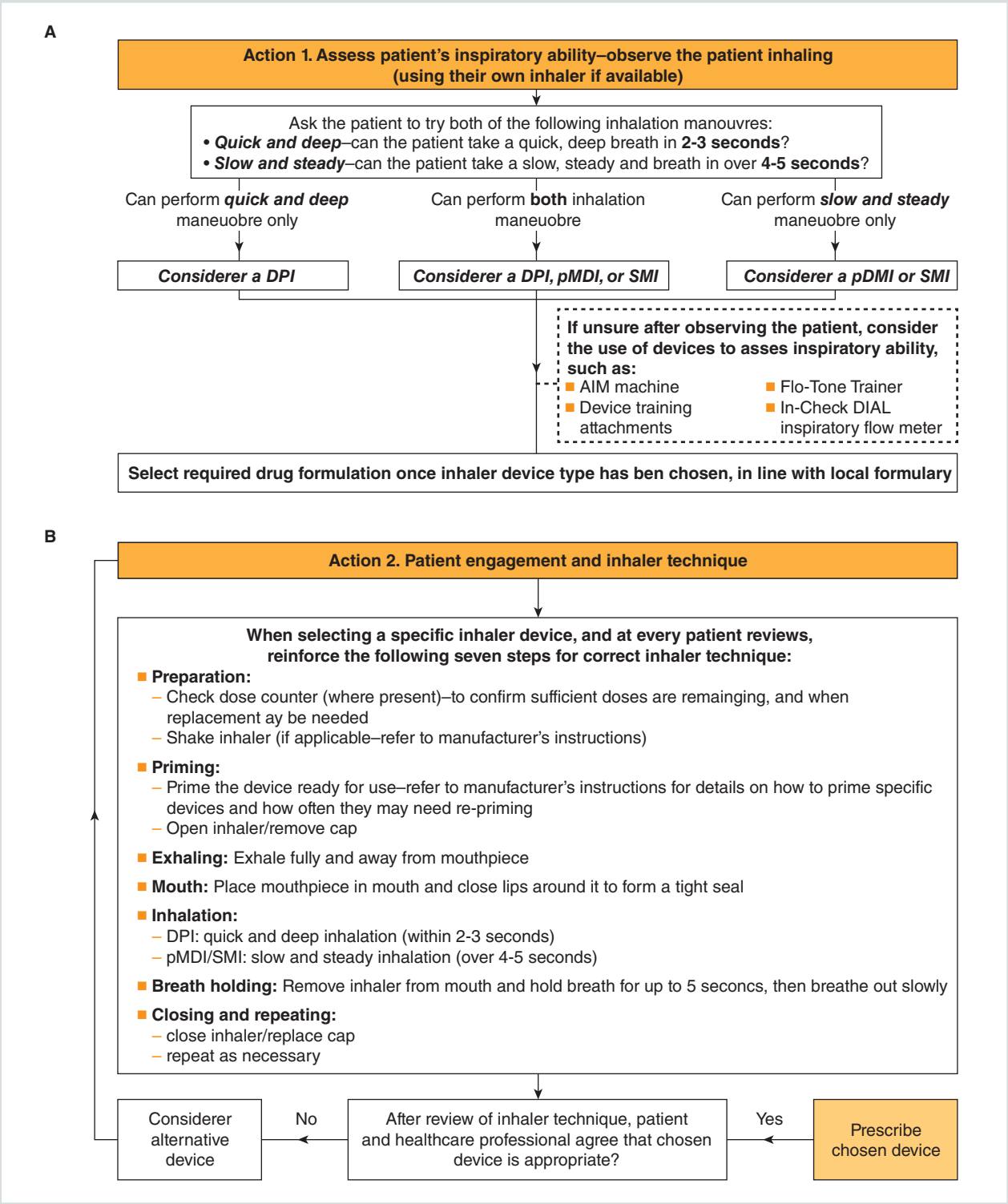

Figure 3. Choosing the appropriate inhaler device for the management of asthma and chronic obstructive pulmonary disease (COPD): a) assess patient's inspiratory ability; b) patient engagement and inhaler technique (from the algorithm developed by MGP Ltd, the publisher of Guidelines and the expert panel by them convened[20]). *Adapted from Usmani O, et al.[78], reproduced with permission.*
DPI: dry powder inhalers; pMDI: pressurised metered-dose inhalers; SMI: soft-mist inhaler.

their proper use[62]. Moreover, changing the inhaler device without the patient's input may result in worsened inhalation technique and critical errors, with a consequent reduction in adherence and disease control[63]. In contrast, choosing an optimal device with effective drug delivery to the lungs, may achieve better adherence, compliance, disease stability and potentially a reduction in the inhaled drug dose without compromising the therapeutic benefit[64]. Indeed, a recent systematic review suggested that practitioners need to consider inhaler devices that can target the deep lung in order to achieve disease control[65].

As with all pharmacological treatment decisions, it is important to actively involve patients in the choice of the inhaler device. Patients are in fact more likely to use a device effectively if they are comfortable with it[66]. Patient preferences regarding inhaler devices have been shown to significantly impact on disease management[67]. Characteristics of inhaler devices that affect patients' perceptions include appearance (size, weight, etc), ease and convenience of use, cost, brand, perceived efficacy, feelings about using the device in public, availability of the drug or device preparations, time needed to learn how to use and clean the device, and disposability/environmental issues[68].

To facilitate good device–patient matching, physicians should be fully educated on device options to enable them to teach their patients proper inhaler technique and advise them on how to avoid common critical errors[69]. In fact, it is strongly recommended that healthcare professionals dedicate time for device education in their clinics and review inhalation technique at each patient visit[70]. With the aim to facilitate this guidance, the evidence or lack thereof underlying ten common 'inhaler lores' beliefs, has been recently reviewed in a practical consensus statement by a panel of experts, on the basis of their combined clinical and research expertise[71].

INNOVATIVE INHALER SOLUTIONS

A variety of innovative strategies and tools are under evaluation and becoming available to improve patient inhaler technique and adherence. Among these, electronic health has shown to be effective in improving quality of care, adherence to therapy and early detection of disease worsening in patients with chronic airway diseases (Fig. 4)[72].

In particular, an increasing body of evidence seems to support the favourable role of inhaler trackers in the management of asthma and COPD. A training device together with a handheld, breath-actuated, microprocessor-controlled accessory has been effectively used in combination with pMDIs, to provide feedback on inhalation flow rate using audible prompts and indication lights[73]. Inhaler sensors to provide feedback to patients and detect environmental triggers that could trigger symptom worsening have been also developed for patients with asthma[74]. The use of monitors that connect to inhalers and provide real-time feedback and/or reminders on the quality of inhaler technique and proper adherence have shown improvements in medication adherence[75]. In a 24-week randomised controlled trial (RCT), the performance of an electronic inhaler device that recorded date, time and number of actuations, was

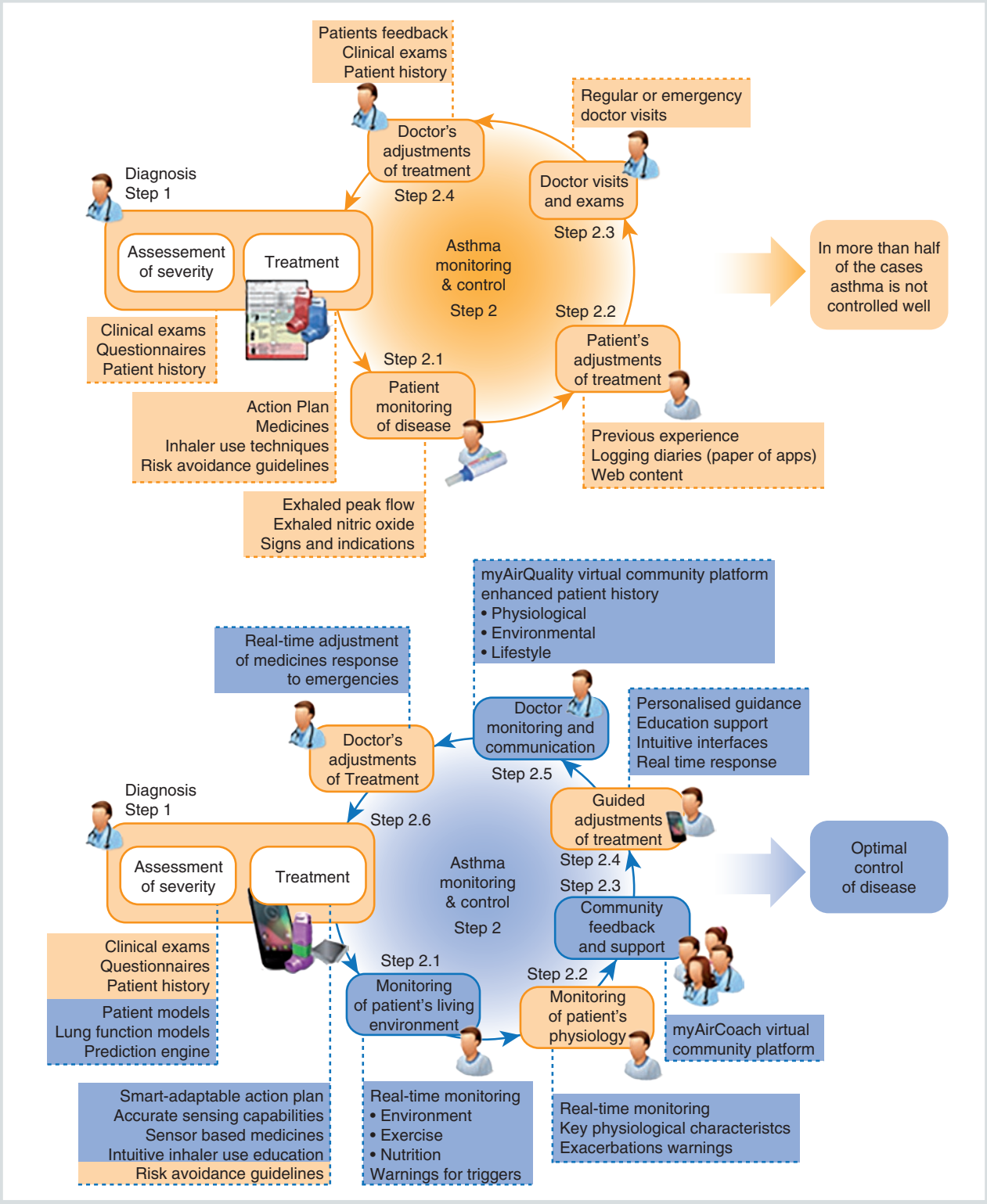

Figure 4. Components of a digital intervention to manage asthma *(reproduced with permission from the myAirCoach EU Horizon 2020 funded project -grant agreement No. 643607; http://www.myaircoach.eu/).* Current standard (in orange) and digital innovative (in blue) approaches to optimally managing asthma.

investigated in more than 300 asthmatic patients. All monitors were loaded with study medication canisters and tested at the coordinating trial site before patient use. Of 2642 monitors dispensed to participants, only 76 (2.9%) failed study monitor checks, 51 (1.9%) malfunctioned before data upload and 93 (3.5%) were lost or discarded by participants, suggesting that electronic monitoring may reliably help to assess patterns of medication use in asthmatic patients by reducing data loss[76]. The accuracy of an inhaler tracker recording actuations from a DPI device (Turbuhaler) was assessed over a 12-week period. The date and time of actuations were recorded in a paper diary and compared with data uploaded from the monitors. On a total of 2800 actuations performed, monitor sensitivity was 99.9% and positive predictive value was 99.9%[77]. The consistency of an inhaler tracker for MDIs was conducted by testing the accuracy of the actuation log and the device functionality (i.e. monitor, buttons, and menu). Patients with asthma trialled the inhaler tracker device for seven days and recorded actuations in a diary. Uploaded data were compared to MDI dose counter and patient diaries. Baseline quality control showed that nine of ten devices had 100% accuracy. Mean actuation log accuracy was 97% and reminders were 100% accurate. All devices successfully uploaded data. Average patient-rated difficulty of use was 6 of 100[78]. In another study, 18 participants from a six-month cluster RCT who received reminders for missed doses via an inhaler tracker adherence monitor were interviewed to explore their feedback on feasibility, utility, and sustainability. Overall, interviewees found the use of reminders and adherence feedback acceptable and useful for improving their adherence and confidence in asthma self-management[79]. Trials conducted with a more robust study design, on wider population samples and with a prolonged length of time are currently ongoing to further inform the debate on whether digital health interventions in asthma help patient outcomes[80].

CONCLUSIONS

In order to demystify inhaler therapy, there is a real need to educate healthcare professionals, particularly doctors, about the importance of each of the inhaler device classes (pMDIs, DPIs, SMIs and nebulisers) used to deliver medication to patients with respiratory disease. There needs to be an appreciation by prescribers, and also patients, that the inhaler device is an integral part of the "drug prescription", and not a bystander. In the constrained time of the consultation with the patient, healthcare professionals need a pragmatic algorithm in choosing the right inhaler device for the right patient and one has recently been published[59]. In prescribing a device, healthcare professionals should take into consideration that a lot of work on inhaled therapies is funded by commercial entities with a vested interest, since this potentially represents a selection bias. Most importantly however, they should have proper knowledge on the key errors in the different device classes that will essentially make the inhaler clinically ineffective. Certainly, recent data show an association between inhaler misuse and worsened health outcomes, highlighting the importance of achieving optimal inhaler technique in the clinic. Additionally, the use of multiple different inhaler device classes is

confusing for patients and should be avoided, as different inhalation manoeuvres are required for each device class, and recent data show multiple inhaler devices adversely affect disease outcomes. An inhaler check at every consultation is recommended as good practice, to ensure patients are not inadvertently increased in the drug dose, when the problem is essentially of being unable to engage with the inhaler device. In the last year, there has been a heightened interest in the role of digital intervention and innovation in managing the chronic airways disease of asthma and COPD. Although some initial studies are encouraging, there is a need for trials to be conducted with robust study design, on wider study samples and with a prolonged assessment time to clearly evaluate whether digital health interventions may significantly help patient outcomes and are cost-effective

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CONFLICTS OF INTEREST

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