EFFECTIVENESS OF INHALER DEVICES IN ADULT ASTHMA AND COPD

Nicolas Roche,[1] Henry Chrystyn,[2] Federico Lavorini,[3] Alvar Agusti,[4] J. Christian Virchow,[5] Richard Dekhuijzen,[6] David Price[7]

1. Respiratory and Intensive Care Medicine, Cochin Hospital Group, AP-HP, University Paris Descartes, Paris, France
2. Division of Pharmacy and Pharmaceutical Sciences, School of Applied Sciences, University of Huddersfield, Huddersfield, UK
3. Department of Experimental and Clinical Medicine, Careggi University Hospital, Florence, Italy
4. Thorax Institute, Hospital Clinic, IDIBAPS, University of Barcelona, Spain; and FISIB, CIBER Enfermedades Respiratorias (CIBERES), Mallorca, Spain
5. Department of Pneumology/Intensive Care Medicine, University of Rostock, Rostock, Germany
6. Department of Pulmonary Diseases, Radboud University Medical Centre, Nijmegen, The Netherlands
7. UK Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK

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ABSTRACT

Inhalation therapy remains the cornerstone of treatment for bronchial diseases. Despite being pharmacologically efficacious, currently available inhaled drugs can have decreased real-life effectiveness due to a variety of factors, including poor inhalation technique. Each device type has its own specifications regarding the optimal way to use it, in terms of device handling and characteristics of the inhalation manoeuvre. Poor inhalation technique is associated with decreased treatment effectiveness. Choosing the optimal device, together with proper education, improves inhalation technique, adherence and outcomes or effectiveness, but has to be performed regularly and rigorously, including visual checking of the patient's ability to use the inhaler. Some testing devices are also available, as well as various training materials. All healthcare professionals caring for the patient can be involved provided that they have also been properly trained. To optimise treatment effectiveness, healthcare providers should prescribe inhalation device(s) optimised to the patient, accounting for the specific characteristics of each individual, his/her disease, and involved healthcare professionals.

Keywords: Asthma, COPD, inhaler, metered-dose inhaler, dry-powder inhaler, technique, effectiveness, education.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are among the most frequently occurring respiratory diseases and represent a major public health burden.[1,2] They are both pulmonary diseases, resulting from interactions between environmental exposures and genetic predispositions. The inhaled route is crucial for their treatment since it allows pharmacological agents (currently, β2-adrenergic and anticholinergic bronchodilators and topical corticosteroids) to be delivered directly to their target receptors while minimising systemic exposure and, thus, side-effects.[3,4]

Several types of portable inhaler devices are now available to administer inhaled drugs, and can be classified in several ways. The first classification differentiates: (1) propellant-driven pressurised metered-dose inhalers (pMDIs), which include standard (i.e. non-breath-actuated) devices, which

can be used with spacers, and breath-actuated pMDIs (BAIs); versus (2) non-propellant-driven dry-powder inhalers (DPIs), which can be multi-dose (with an integrated reservoir) or single-dose (using capsules). An alternative classification differentiates devices that require accurate coordination between triggering and inhalation (i.e. pMDIs without spacers) and those that were developed to alleviate the need for proper coordination, i.e. spacers, BAIs and DPIs.[5] Among pMDIs, devices delivering HFA-propelled extra-fine particles have been developed. These devices increase deposition in small airways and reduce the influence of errors in coordination and inhalation flow.[6,7] Nebulisers are not discussed here since they are considered as second line devices for long-term treatment of asthma and COPD.[1,2]

The important characteristics of the dose emitted include the mass median aerodynamic diameter (MMAD) and the fine particle dose (FPD). The MMAD provides an understanding of the size of the emitted particles, with those <5 μm being the most likely to be deposited into the airways. The FPD is the amount of particles with a size <5 μm.[5]

The effectiveness of inhaled treatments is influenced by several factors, including: (1) their efficacy, i.e. their positive effects when used under optimal conditions, directly resulting from their pharmacological properties; and, (2) the way they are used, i.e. the appropriateness of prescription and patients' adherence and ability to use inhalation devices. A systematic review of efficacy studies (i.e. randomised controlled trials) performed a decade ago did not find significant differences between devices.[8] Usually, patients were highly trained regarding their inhalation technique and those who did not demonstrate correct use post-training were excluded. Thus, the real-life effectiveness of the various available devices is not known and could be markedly influenced by the way they are used. A systematic review, by Brocklebank et al. in 2001, underlined the need for additional studies aimed at determining whether some differences between devices can be identified in terms of effectiveness.[9] Some studies have been conducted thereafter to address this issue.[10,11]

Misuse of inhalers will prevent the pharmacological agent from reaching its target, resulting in a decreased effect.[12] The amount of drug depositing in the lung depends on three factors: the drug formulation, the technical characteristics of the device (such as its external and internal design and, for DPIs, the resistance to inhalation), and the ability of the patient to handle it and inhale properly (Figure 1).

Many studies have investigated the frequency and consequences of inhaler misuse. Their results support the major importance given to inhaler technique as a determinant of treatment success. However, only few guidelines address the issue of inhaler technique in detail.[5,13] As a consequence, several international groups developed a specific interest for research and communication on this topic, such as the Asthma Drug Management Team (ADMIT) (http://www.admit-online.info/en/), and the recently established Respiratory Effectiveness Group (REG), (http://www.effectivenessevaluation.org/).

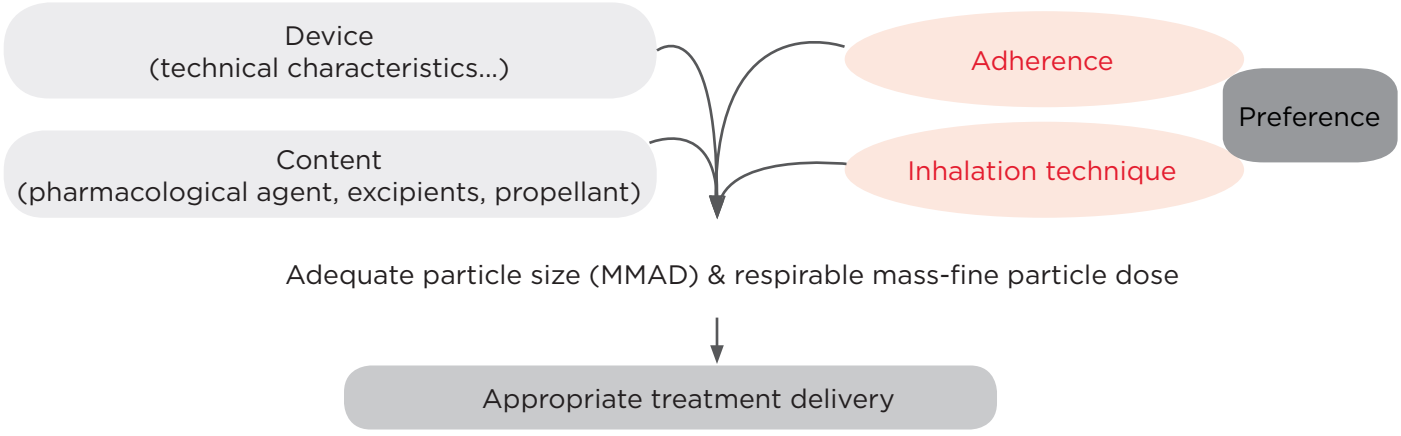

Figure 1. Basic principles in inhalation therapy: factors that influence the effectiveness of inhaled medications. MMAD: mass median aerodynamic diameter. Fine/respirable particles: MMAD <5 μm.

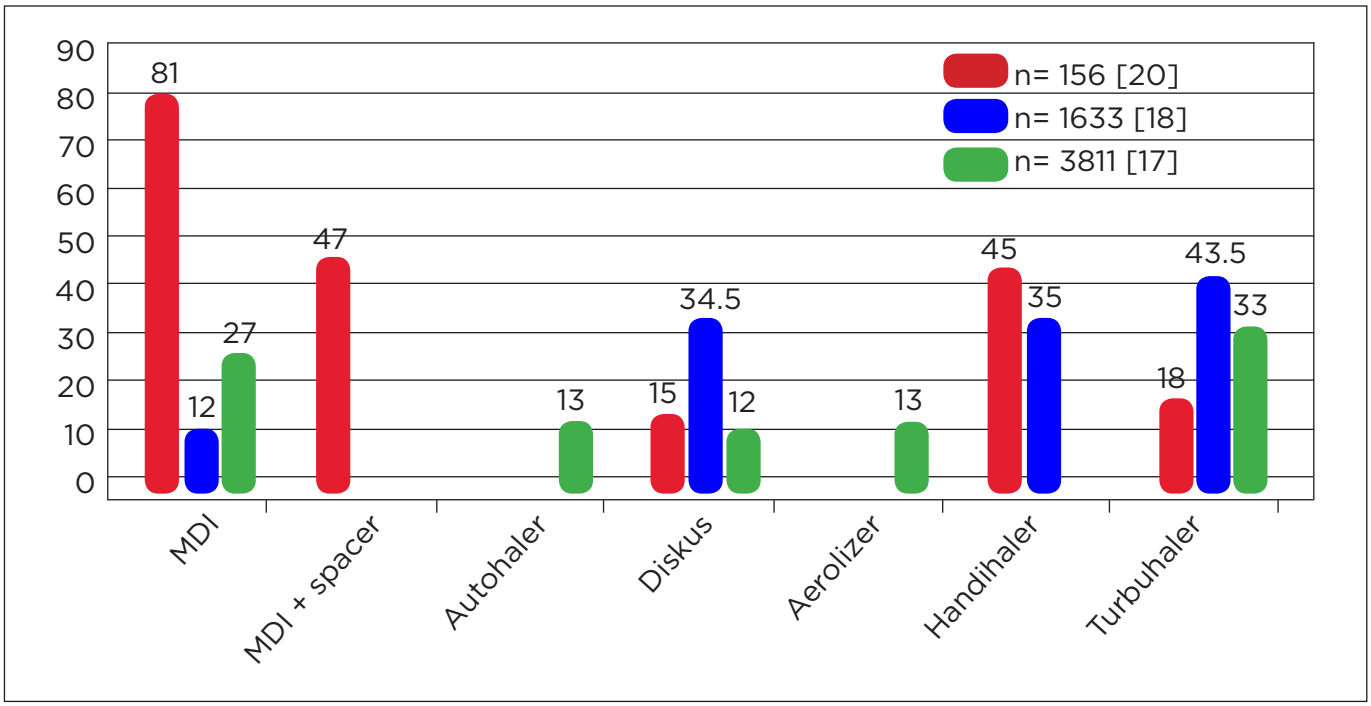

Figure 2. Frequency of inhalation errors by device type. Data from three studies.[19,20,22]

BASIC PRINCIPLES OF INHALER USE

The following steps of inhaler use are common to all devices: (1) device preparation (shaking for some pMDIs, adaptation to the spacer when required, priming for BAIs and reservoir DPIs, capsule insertion for single-dose DPIs); (2) exhalation followed by deep inhalation (coordinated with device triggering for pMDIs); (3) breath-holding (lasting at least 4 seconds); and, finally (4) normal breathing lasting at least 30 seconds before repetition of all these manoeuvres when a second dose is required. With pMDIs and BAIs, the drug formulation is propelled by the pressurised gas contained in the cartridge when the device is actuated, either manually (pMDIs) or automatically when inhalation begins (BAIs). Therefore, the main initial driving force is propulsion by the pMDI device and, as such, the inhalation needs to be slow. In contrast, when using DPIs, the only driving force is inhalation. The formulation of a DPI is broken up (de-aggregated) during the first part of each inhalation into particles that have characteristics suitable for deposition into the lungs (i.e. a diameter of <5 μm). This break-up is caused by a turbulent force that is generated inside the DPI by the interaction between the patient's inhalation and the resistance of the device. Each DPI has its own resistance ranging from low to high.[5] To obtain a set inhalation flow with higher resistance, the patient needs to use a more forceful initial inhalation.[14] Hence, compared to a pMDI, the inhalation manoeuvre from a DPI needs to be forceful, which many translate to 'as fast as you can'. Since the break-up of the dose occurs in the first part of the inhalation, the instruction with a DPI is 'forceful from the start'. Together with the intrinsic aerodynamic properties of drug particles, this explains why inhalation should preferentially be slow with pMDIs (especially to limit oropharyngeal impaction), while it has to be fast from the beginning with DPIs.[15-17] These inhalation manoeuvres are required to provide ideal inhalation flows of 30 L/min for pMDIs and between 30-90 L/min for DPIs. Finally, to ensure good penetration into the lungs, a deep inhalation manoeuvre is required and is usually defined as lasting at least 4-5 seconds.

FREQUENCY AND DETERMINANTS OF INHALER MISUSE

All studies in this area agree on a high proportion of misuse among patients with asthma or COPD, even in those who had been exposed to devices for long periods.[18-22] However, the frequency of misuse for each particular type of device varies between studies, depending on the studied population and

on the criteria used to define proper technique. Figure 2 combines results from some of these studies. Altogether, standard pMDIs are definitely the devices with the highest proportion of errors, but misuse is also frequent with the other types of devices; these have been developed to limit the impact of poor coordination but still need proper preparation, inhalation and breath-holding. Preparation errors relate, for example, to improper device priming manoeuvres including improper device position. Thus, none of the devices currently available can be considered as 'ideal' in that all require some patient skill. As a consequence, training is always required to ensure adequate patient education about specific handling requirements, as well as on the inhalation technique per se.[5]

Some patients appear to be at higher risk of poor inhalation technique.[22,23] Some risk-factors relate directly to the patient, these include: extreme ages (i.e. young children and the elderly), very severe airflow obstruction, cognitive dysfunction, motor handicap of the upper extremities, and co-morbidities such as stroke etc. In addition, patient preference could be associated not only with compliance but also with inhalation technique.[24] Other risk factors relate to the prescription and delivery of the treatment: patients who are simultaneously prescribed different types of devices (e.g. a pMDI and a DPI)[25] tend to use their devices less appropriately than those using a single device type (although some controversial data on this topic have been published in children),[26] and device switching without a face-to-face review is associated with worsening of asthma control.[27] The last group of risk factors relates to measures that should accompany the prescription: patients are to be trained on the optimal way of using their device, and inhalation technique has to be checked regularly. Virtually all healthcare professionals can be involved in patient training and follow-up regarding inhaler technique: primary care physicians, lung specialists, pharmacists, nurses, and physiotherapists. Since healthcare providers' skills and knowledge of inhalers can also be poor, they require training on correct inhaler handling.[28]

IMPACT OF INHALER MISUSE ON TREATMENT EFFECTIVENESS

Clinical consequences of poor inhalation technique have been studied mostly in asthma, where it is easier to explore links between inhaler use and control. Such studies are more difficult in COPD due to the very progressive nature of the disease and relatively small magnitude of observable treatment effects in the short-term.

It has long been known that pMDI misuse decreases the amount of drug deposited in the lungs and that, in patients with poor coordination, deposition can be improved by the use of spacers, BAIs or DPIs.[29] Corresponding studies used mostly scintigraphy with Technetium-radio-labelled particles as a means to provide images showing the level of deposition in the device, throat, lungs, and stomach.[30] Others have measured blood levels of administered drugs or their metabolites, blocking digestive absorption with charcoal so that systemic exposure results from lung absorption only, which directly correlates with lung deposition.[31] It has also been demonstrated that the magnitude of bronchodilation, obtained by β2-agonists, decreases in poor users.[32] Finally, more recent studies managed to show a link between poor inhaler technique and poor asthma control.[18,33-35] In one of these studies, a "dose-dependent" relationship was even found between the number of errors in pMDI use and the level of control (named "instability" at that time).[18] Asthma control was worse in poor pMDI users and, among errors in inhalation technique, poor coordination had the greatest impact on control. More recently, these authors found a triangular relationship between control, adherence to treatment and inhaler technique.[33] Poor inhalation technique and poor compliance were both independently associated with control, the other risk factor for poor control in that study being smoking.

Altogether, these results show that inhalation technique should belong to the systematic check-list when assessing a patient with insufficient asthma control, together with smoking status, other environmental exposures (to allergens or irritants), body mass index, adherence to treatment, associated diseases, or an alternate diagnosis (gastro-oesophageal reflux, COPD, hyperventilation syndrome, vocal cord dysfunction, congestive heart failure, vasculitis, allergic bronchopulmonary aspergillosis).[36,37]

COMBATTING INHALER MISUSE TO IMPROVE TREATMENT EFFECTIVENESS

Three directions can be followed to decrease the frequency and consequences of poor

inhalation technique: research to improve inhalers, training patients and doctors, and individualising inhaler choice.

Developing the 'Ideal Inhaler'

The ideal inhaler would be user-friendly, delivering optimal respirable amounts of drugs irrespective of the prescriber and patient's skills, without any need for external supervision and independently of environmental conditions. More realistically, it should have the characteristics described in Table 1. To date, none of the currently available inhalers can be considered as 'perfect' regarding all these characteristics. All need some training and regular checking of inhalation technique. However, some new inhalers try to simplify required manipulation. It must also be noted that most devices still do not deliver all pharmacological classes of respiratory drugs. Thus, the choice of the prescribed pharmacological agent restricts (and can be restricted by) the number of devices that can be proposed.

Checking and Training

Several observational studies have shown that training patients on inhaler use improves not only inhalation technique but also adherence to treatment and, most importantly, disease control.[15,33,38,39] Most of these studies are purely observational with a 'before-after' design, and include only patients with asthma. Only a few specifically recruited patients with COPD, in whom similar improvements were demonstrated.[39] Interestingly, one observational study found that control improved only in those patients in whom inhaler technique improved following training by pharmacists, suggesting that the effect of training on control is actually determined by its effect on inhaler technique.[33] Similar results were very recently found in COPD patients.[40] However, it has also been shown that the effect of training is inconstant and sometimes transient.[41]

Several tools and strategies can be used to provide training: visits to health care professionals using placebo demonstration devices or the patient's own device, video demonstration of adequate and incorrect technique, tele-counselling,[42] and web-based programs.[43] As mentioned above, all healthcare professionals should be involved in this training process: primary care physicians, lung specialists, nurses, physiotherapists, and pharmacists. The choice of tools and involved professionals often depends on local availability and organisation. It is also of utmost importance to educate professionals properly in the first place[44] and then repeat training regularly.

In all cases, it must be outlined that providing patients with written material (such as brochures and leaflets) is not sufficient. A critical step in education is the regular observation of the patient using his/her inhaler. The other major step is the live demonstration of proper technique when necessary, followed by repeated observation of the patient's ability to correct his/her technique. Simply asking the patient whether he/she has difficulties using his/her inhaler does not provide reliable information.[21]

Table 1. Theoretical characteristics of the ideal inhaler.

Criteria	Device and inhalation technique characteristics
General appearance	User-friendly
Priming	None
Coordination between triggering and inhalation	Not required
Effect of errors in inhalation technique	None
Dose consistency	Perfect, independently of environmental conditions (temperature, humidity etc) and inhalation manoeuvre
Dose counter	Present, based on actual inhalation rather than manipulation
Perception of drug delivery	Clear perception (but not based on unpleasant sensations such as bad taste)
Feedback	Confirmation that a dose has been inhaled, technique used was correct Reminder about adherence

Of note, some testing and training devices have been developed to help healthcare professionals check inhalation technique and train patients.[15,41] They are known to improve inhalation technique, but their cost-effectiveness remains unknown at present. In addition, no study has investigated the effect of training or the most desirable training method/tool in situ over a prolonged period of time.

Personalising Device Choice

Patients with asthma or COPD do not all require the same treatment, and do not all have the same skills and preferences. Therefore, tailoring the treatment to each specific patient is of utmost importance.[3,45-49] Several factors have to be taken into account when selecting a specific inhaler device for each patient. These factors can be categorised in four ways: (1) Patient-related factors, including (i) age and ability to inhale consciously, handle the device and coordinate the use of the device and the inspiratory effort, (ii) patient's preference, (iii) adherence and compliance, (iv) language and literacy, and (v) presence of comorbidities that could be aggravated by some respiratory treatments. (2) Disease-related factors, since (i) severe and/or acute airflow obstruction may compromise the ability to generate an adequate inspiratory flow and (ii) therapeutic strategy and indications are not the same for asthma and COPD. (3) Device-related factors, as the optimal inhalation profile differs between pMDIs (slow inspiration is preferable) and DPIs (forceful high-flow inhalation is not required, with fast acceleration especially for reservoir devices). For example, observational comparative effectiveness studies suggested that BAIs and standard pMDIs (using HFA-propelled extra fine particles with a size of approximately 1 μm) could improve treatment effectiveness as compared to standard metered-dose inhalers,[7,8] due to the more limited influence of errors in coordination/inhalation technique on lung deposition with these devices.[6,7] Finally, (4) Caregiver-related factors, accounting for the availability and knowledge of professionals involved in information and education (general practitioners, specialists, nurses, physiotherapists, pharmacists).

In addition, the multiplication of inhalation devices and corresponding instructions should be avoided since it can be a source of confusion for healthcare providers who are not specialised in the respiratory area, such as many primary care physicians, even though they care for the majority of patients with asthma or COPD.

CONCLUSIONS

The inhaled route remains crucial for the treatment of bronchial diseases. However, drug deposition and subsequent treatment effectiveness are highly dependent on inhalation technique, which is incorrect in many patients with asthma and COPD. Many inhalation devices are available and others are currently being developed with the aim of simplifying required handling, and thus improving treatment safety. Nonetheless, at present, proper training and regular checking of inhalation technique remain critical to optimise treatment effectiveness. Involved healthcare professionals have to be adequately trained before providing this service. Various educational tools can be used including videos, web-based platforms, and tele-counselling. Optimising treatment effectiveness also requires tailoring the drug-device combination chosen for each individual patient, based on his/her individual characteristics, the specific disease and its severity, the characteristics of devices, and the skills of involved healthcare professionals. There is a need for long term effectiveness studies to identify the training methods/tools that should be used for each inhaler.

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JCV has lectured for a received honoraria from Asche-Chiesi, AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer-Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergens, TEVA, UCB/Schwarz-Pharma, Zydus/Cadila and possibly others and has participated in advisory boards for Asche-Chiesi, Avontec, Boehringer-Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, MSD, Mundipharma, Novartis, Revotar, Sandoz-Hexal, UCB/Schwarz-Pharma and possibly others and has received grants from GSK, MSD, and the Deutsche Forschungsgemeinschaft.

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