Inhalatory therapy training: a priority challenge for the physician

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Abstract. Patients with asthma and COPD commonly use inhaled drugs. The 3 types of currently available devices for inhaled therapy (Metered-dose inhaler, dry powder inhaler, and nebulizer) are clinically equivalent. However, since many different inhalers are available for inhaled therapy, the choice of the delivery device is important for optimizing the results of aerosol therapy.Traditional press-and-breathe Metered Dose Inhalers (pMDIs) have recently improved their ecological appeal, can be used in every clinical and environmental situation, their dosing is convenient and highly reproducible, but their efficient delivery remains highly technique dependent. Poor inhalation technique can be minimised by the use of add-on valved holding chambers, which are seldom used in the clinical practice possibly because they are cumbersome. Breath Actuated devices (BAIs), such as Dry Powder Inhalers (DPIs), which are environmental-friendly, safe, effective, reliable, portable and self-contained, overcome problems of handbreath co-ordination associated with pMDIs usage, but their use is also undermined by common errors of inhalation technique in real life. Nebulizers are cumbersome and time-comsuming for use and maintenance, but their use needs less cooperation than inhalers. Although nebulizer practice is not always evidence-based, some patients, mainly elderly prefer nebulizers for regular long-term usage. Despite the introduction of newer devices, clear advantages of a particular delivery system over other inhalers in terms of compliance, preference, and cost-effectiveness are not currently available. The objective of an ideal and easy-to use inhaler is far from reality. Patient education is the critical factor in the use and misuse of delivery devices and effectiveness of aerosol therapy. The choice of the device has to be tailored according to the patient's needs, situation, and preference.Whatever the chosen inhaler, education from health caregivers has a key-role for improving inhaler technique and compliance. Differences among delivery devices represent another challenge to patient use and caregiver instruction. (www.actabiomedica.it)

Key words: Inhaler, nebulizer, asthma, COPD, spacer, aerosol administration, drug delivery, compliance, clinical practice

Introduction

Nowadays the most common chronic bronchopulmonary diseases, such as asthma and COPD, are mainly treated by inhaled therapy (1-3). It is interesting to note that this practice became widespread many years after the introduction (through other administration routes) of atropine and adrenaline, the prototypes of the most widely used bronchodilators (4), only when efficient nebulizer ampoules (5) and inhalers (6, 7) finally became available.

Physicians currently have a choice of 3 types of dispensers for lung deposition of drugs: A) nebulizers, B) pressurized inhalers and C) the dry powder inha-

lers; many models of each type are available, all of them with advantages and disadvantages (Table 1), but none with ideal properties (Table 2).

Unfortunately the physician often simply prescribes inhaler therapy, taking for granted that the patient will carry it out properly, whereas the majority of patients does not realize that the efficacy of inhaler therapy often depends on whether it is carried out correctly.

On the other hand, not only does the National Health Services not support educational activities which aim to teach patients how to correctly use the prescribed inhalers, but they do not even request minimum efficacy requirements to enable new aerosol therapy devices to be marketed and they also supply generic drugs for inhalation use by referring only to the active ingredient and not to the inhaler delivering it.

Pressurized inhalers

The metered-dose pressurized inhalers (hereinafter "spray") are pocket-sized, scarcely affected by environmental influences, work autonomously, are efficient, and contain and accurately deliver many doses of aerosol in a short time. Although many types of sprays are available on the market with very different characteristics, the shape, the dimensions and the mechanism of action is substantially similar for all of them (apart from the types, of which only the Autohaler® is available in Italy, in which the aerosolization is determined by the user's inhalation once the delivery device is switched on) (8, 9). Despite this apparent immutability, a great effort has been recently made to replace the old chlorofluorocarbon propellants (CFC), since they are not environmentally friendly, with the new hydrofluoroalkanes (HFA), which ensure a lower environmental impact (10). This means that new formulations have been produced which have partly contributed to the improvement of some characteristics (e.g. lower granulometry, less need to coordinate delivery-inhalation) (11-19). A counter has been inserted in the salmeterol/fluticasone combination in order to identify the remaining doses of aerosol (Fig. 1). This is an undoubted practical advantage compared to the traditional sprays (20), for which the only way of avoiding the risk of delivering an aerosol with less or no active ingredient by exceeding the inhaler's stated dose limit (24), was to keep a tally (rarely done) of the doses already delivered (21-23).

The sprays main limitation was and is still linked to the fact that many patients cannot use them correctly (Table 3), and this can reduce or even eliminate the potential for clinical efficacy (25, 26). More than 30 years ago Crompton (27) estimated that approximately half of all users were unable to use the sprays carried out and the current situation appears to be little improved (28): in a recent study conducted in a pneumology department in Italy on a sample of adult pa-

Table 1. Main properties of nebulizers and inhalers

Characteristics	Nebulizers	Inhalers (both pressurized and dry powder types)
Retail sales method	Drug and device sold separately	Drug and device sold together
Accurate drug delivery with optimal use	Light	Good
Aerosolization time	Long (several minutes)	Short (few seconds)
Need for maintenance	After each use	No
Weight	Varies, but always significant	Light (few grams)
Dimensions	Vary, but not pocket-size	Pocket size
Active cooperation required by user for optimal use	No	Yes
Operating method	Requires external energy source	Autonomous
Availability	With every drug	With some drugs

Table 2. Characteristics of an ideal inhaler

Little oropharyngeal deposition of drug
Excellent lung deposition of drug
Lightweight and pocket-sized
Little or no unfavourable ecological impact
May be used in all clinical and environmental circumstances
May be used without the need for accessories and/or external power sources
Must contain enough drug for many aerosolizations
Possibility of counting the delivered and the residual doses
Little or no possibility of the degradation or contamination of the active ingredient with use
Ease of use without or with minimum need for collaboration by user or the caregiver and system for checking whether optimum aerosolization of the dose has taken place
No additives, propellants or excipients
Active ingredient accurately released in each dose and in all environmental conditions
It must quickly aerosolize the dose of the drug, with the possibility of repeating the delivery if necessary several times immediately afterwards
Needs little or no maintenance
May be used with any drug which has potential clinical efficacy when administered via aerosol
Good cost-effectiveness

tients who had been using the sprays at home for some time, the frequency of errors of inhalation technique which significantly or completely reduce lung deposition of the aerosolized drug (defined as critical errors below), was approximately 20% of the total (29).

An alternative technique for those who cannot manage hand-breath coordination is the addition of a spacer to the spray. There are various types of spacers, all distinguished by the characteristic of adding "volume" between the canister and the user. The best results are obtained with spacers provided with one-way valves. The user inhales the aerosolized drug in the spacer but does not exhale into it (Fig. 2) (30). Spacers are also useful for administering the drugs by inhalation to non-cooperating subjects or those on a ventilator, since less of the active drug impacts on the oropharyngeal area and more is deposited in the lungs. However, the use of spacers remains limited, perhaps because they are cumbersome, meaning that the spray is no longer pocket-sized: in 2000, the percentage of adults treated in pneumology departments in Italy using inhalation chambers was slightly less than 18% of the total number of subjects using sprays (29), whereas a larger number, approximately 35% was reported for asthmatic children treated by pediatricians (31).

Figure 1. Metered-dose pressurized inhaler with dose counter for delivery of the salmeterol/fluticasone propionate combination

Another disadvantage of the spacer chambers is the need for routine maintenance with a standardized procedure (washing with water and washing up liquid is recommended at least once a week, followed by leaving it to dry instead of drying it with a cloth!) in order to reduce the electrostatic charges which may unfavourably interact with the aerosol delivered; some new spacers, such as the NebuChamber®, Vortex®, Fluspacer®, OptiChamber® or AeroChamber Plus®, develop these negative interactions less frequently (30, 32).

Dry powder inhalers

Just like the pressurized inhaler, dry powder inhalers are pocket sized, efficient and do not require any external source of energy to deliver the aerosol. Unlike the sprays, which are substantially all characterized by a similar exterior appearance and operating procedure,

Table 3. Spray inhalation techniques: percentage of errors in real life compared to the recommended procedure and clinical consequences

Phase of recommended inhalation technique	Percentage of non-compliance with the recommended procedure	Clinical consequence of non-compliance
Removing the cap from the mouthpiece	+	X
Shaking the inhaler immediately before use"	++	-
Emptying or almost emptying the lungs before activating the spray	+++	-
Placing the mouthpiece in the mouth, closing lips around it and avoiding any obstruction by the tongue; or placing the mouthpiece approximately 3-4 cm in front of the mouth, which is kept wide open	+	from - to X
Keeping the spray with the longest part pointing upwards during delivery	++	-
Activating the inhaler once only with a single inhalation[$]	++	-
Activating the inhaler during the first half of inhalation	+++	from -- to X
Slowly inhaling while activating the inhaler	+++	--
Continuing to fill the lungs completely without stopping after delivery of the dose	+++	--
Holding breath for at least 8-10 seconds or for as long as possible when inhalation is complete	+++	--

$ = if the spray had not been used in the previous 3-4 days, it is advisable to deliver 1-2 puffs without inhaling; Noncompliance reported occasionally = +; Noncompliance reported quite frequently (up to 20-25% of the total) = ++; Noncompliance reported frequently (up to and more than 50% of the total) = +++; Clinical consequence of this variety of misuse is slight = -; Clinical consequence of this variety of misuse is moderate = --; Critical error, such as to reduce drug lung deposition totally = X

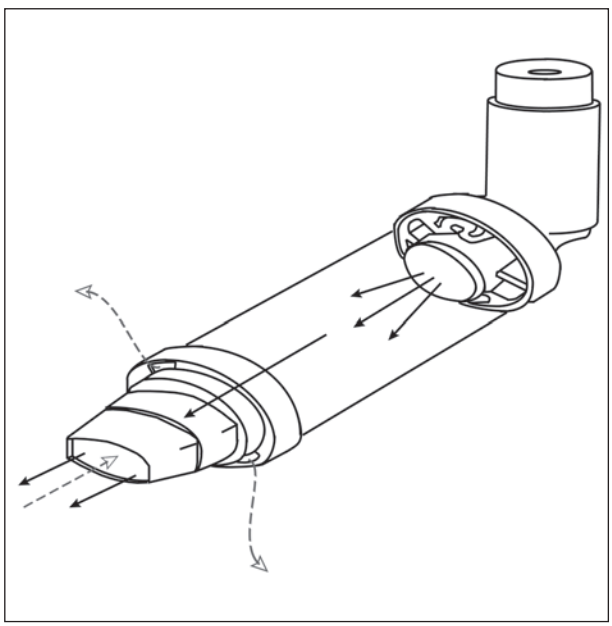

Figure 2. Example of spacer chamber (with a one-way valve to ensure the content of the chamber is inhaled, while the exhaled air is directed outside, as indicated by the arrows)

the various dry powder inhalers differ due to morphology (Table 4) and method of use.

Technical errors in use made by patients instead of the recommended procedure, have also been reported for the dry powder dispensers (Tables 5, 6). Some are single-dose systems, in which the drug is contained in a capsule which must be inserted in the appropriate housing of the dispenser each time immediately before inhalation. Others, known as multiple-dose di-

Table 4. Dry powder inhalers currently marketed in Italy

Inhaler	Drugs dispensed
HandiHaler	Tiotropium
Diskus	Salmeterol, fluticasone,
Turbohaler	Formoterol, budesonide, formoterol/ budesonide, terbutaline
Aerolizer	Formoterol, budesonide
Novolizer	Budesonide
Pulvinal	BDP

Table 5. Inhalation technique with single-dose dry powder inhaler: error percentage in real life compared with the recommended procedure and clinical consequences (25)

Inhalation technique phase	Percentage of non-compliance with the recommended procedure	Clinical consequence of non-compliance
Removing the cap	+	X
Opening the appropriate inhaler housing inserting the capsule immediately before use and closing it correctly	+	from - to X
Pressing the buttons situated at the base of the inhaler at the same time in order to break the capsule containing the drug	+	from - to X
Emptying the lungs to avoid exhaling into the inhaler after breaking the capsule	++	--
Placing the mouthpiece in the mouth, closing lips around it and avoiding any obstruction with the tongue	+	from – to X
Inhaling with maximum inhalatory force from the start	+++	from – to X
Stopping inhalation only after filling the lungs completely	++	-
Removing the inhaler from the mouth without exhaling into it	++	-
Checking whether the capsule is empty after use and if there is still some powder, repeating the inhalation, removing it, closing the mouthpiece and replacing the cap	+	-
Closing the inhaler	+	-

+; ++; +++; -; —; X = *see key Table 3*

Table 6. Inhalation technique for multiple-dose powder inhaler: error percentage in real life compared with the recommended procedure and clinical consequences (25)

Inhalation technique phase	Percentage of non-compliance with the recommended procedure	Clinical consequence of non-compliance
Removing inhaler cap/opening the dispenser	+	X
Loading the dispenser sufficiently°	+	X
Emptying the lungs, avoiding exhaling into the inhaler after loading	++	--
Placing the mouthpiece in the mouth, closing lips around it and avoiding any obstruction with the tongue	+	from – to X
Inhaling with maximum inhalatory force from the start^	+++	from – to X
Stopping inhalation only after filling the lungs completely	++	-
Removing the inhaler from the mouth without exhaling into it*	++	-
Closing the inhaler	+	-

*°In some cases this phase is position-sensitive, for example the Turbohaler's longest axis must be arranged vertically or at an angle no greater than 15-20° out of the vertical; * for reservoir inhalers such as the Turbohaler, the humidity of the exhalation can cause the powder to clump and worsen aerosolization in subsequent inhalations; ^especially with Turbohaler which contains little or no excipient, the user must be warned that even well-performed inhalations may not be accompanied by any perception or taste in the mouth; see key Table 3*

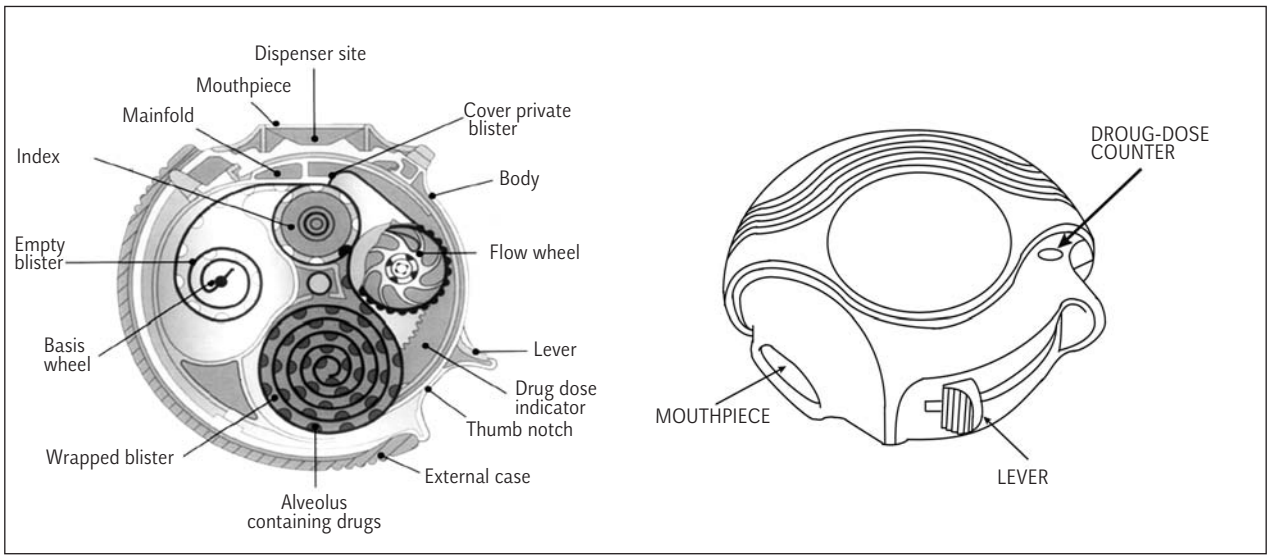

Figure 3. Multiple-dose dry powder inhaler (Diskus), the arrow on the right indicates the dose-counter

spensers, contain enough drug in the inhaler for many deliveries; each dose may be ready for use (the prototype is the Diskus®), (Fig. 3) (33), or may be drawn from a reservoir while loading (the prototype for these systems is the Turbohaler®) (34).

All the multiple-dose powder inhalers include systems (more or less sophisticated) which count the doses administered and those remaining. Just like the sprays, the dry powder dispensers do not require any proper maintenance, but only regular cleaning.

The main advantages of the dry powder inhalers over the sprays are shown as follows:

a) they are ecologically compatible, they do not require propellant for aerosolization;
b) they are activated when the user inhales and do not require any hand-breath coordination

The main disadvantages are:

a) they are impossible to use in non-cooperating patients, or in those who are ventilated or tracheostomized, or to add a spacer to;
b) the aerosol drug output (35) is less accurate and reproducible, especially in a situation with high humidity and high surrounding temperature (36-39), particularly in the multiple-dose, reservoir devices such as Turbohaler;
c) the fear that patients with serious ventilatory impairment would not be able to generate the flows and volumes required for adequate inhalation: this can happen in the case of children or patients in more serious clinical situations, especially when high-resistance dispensers such as HandiHaler or Turbohaler are used (40-42).

Nebulizers

Nebulizers are essentially able to convert any liquid into an aerosol. There are two fundamental classes of nebulizers: mechanical nebulizers – which amount to no less than 90% of the total used at home for pneumological reasons (43) – and the ultrasound types. Numerous models are available on the market for each class, even though none of them comes close to the ideal device (Table 7) (44).

It is important to remember that very few studies have been carried out with strict methodologies to compare the characteristics of the various nebulizers, but where data is available, it reveals substantial differences between the different models regarding both aerosol emission and the dimensions of the particles emitted (45).

The traditional ultrasound types are very compact, less noisy than the mechanical types and provide a greater aerosol output per unit of time (46), but are

Table 7. Main characteristics of an ideal nebulizer

High aerosol output per unit of time
High efficiency
Reproducible performance in different operating conditions
Reduced energy consumption when functioning
Easy to use
Possibility for the patient to check whether the nebulization was carried out correctly and the system was operating optimally
Easy, reduced maintenance
Not cumbersome
Robust
Little noise

not recommended for nebulizing corticosteroids (47). The mechanical nebulizers usually include a compressor (more often in hospitals the source of compressed gas is centralized with wall-mounted connection devices available), a nebulizing ampoule, an interface with the patient (mouthpiece or nose mask), and the tubes connecting these different components; only recently all these components were made into a more compact system, such as the Clenny®, although still not pocket-sized. The nebulizer ampoule is the essential part of the mechanical nebulizer; some are made of glass (not recommended!) and some in plastic; single-use versions, which generally work well for several nebulizations, and reusable versions, can remain efficient for up to a year if suitably maintained. The traditional ampoules continuously produce the aerosol which is only inhaled when the user breathes in, leading to a considerable waste of nebulized drug; nowadays, the introduction of additional openings in the ampoules, provided with one-way valves which allow the passage of air during inhalation but not during exhalation, selectively increases the aerosol emission and the percentage of fine particles; these ampoules, known as breath-enhanced ampoules, are available on the market at only a slightly higher cost than the traditional ones, and are recommended if expensive drugs such as cortisone need to be repeatedly nebulized. A good nebulizer should complete a single nebulization in less than 10 minutes (48), whereas GENebu studies conducted in Italy in 1999 on adults who used a nebulizer at home, showed that the duration of an individual nebulization exceeded 15 minutes in 36% of cases (43); this confirms the need for significant training in this field.

Solutions and suspensions may be distinguished according to the level of solubility of the drug in the solvent: bronchodilators are habitually formulated as solutions and nebulize relatively simply, the cortisones, in suspensions, have greater requirements (the ampoule for which there is evidence of clinical efficacy is the Pari LC Plus® with budesonide) for nebulization (47). The possibility of mixing more drugs in a single nebulization is a widespread practice used both at home and in the hospital (49): most nebulizer use at home in Italy includes mixtures of several drugs, almost always including corticosteroids (43). From the limited available data it seems that, if the beta-agonists are mixed with the anticholinergics immediately before nebulization, there are no negative interactions, such as between bronchodilators and mucolytics or antimicrobics, but mixing mucolytics and antimicrobics may have a negative influence on the nebulization of the latter (50).

Studies carried out by the manufacturer do not report any negative interactions when budesonide is mixed with bronchodilators (51), but mixing beclomethasone diproprionate (NDP) or flunisolide with bronchodilators *in vitro* considerably reduces the percentage of breathable particles compared with nebulization of the individual active ingredients (52, 53).

Buffers and antibacterials, which can sometimes cause bronchoconstriction that may be severe, are often added in order to increase the half-life of the formulations and to reduce the risk of contamination.

The risk of contamination by microorganisms in nebulizing aerosols has been known for many years; the cause of the contamination has often been attributed to the use of multiple dose solutions of drugs and solvents or to the watery residue which remains in the ampoules if they are not regularly dried after each nebulization. Contamination is often due to particularly insidious germs such as *Pseudomonas aeruginosa,* methicillin-resistant Staphylococcus aureus *Burkholderia cepacia*, and *Stenonotrophomonas maltophilia* (53).

Unfortunately regular nebulizer hygiene procedure is rarely carried out, both in the hospital and at home. Data from the GENebu Project show that approximately 60% of adults have never received instructions on nebulizer maintenance from physicians, even though the fact that patients who had received such instructions carried out hygiene procedures more often, was reassuring (54).

In order to reduce the risk of the bacterial contamination of therapeutic aerosols it is necessary to carry out the regular cleaning and disinfection procedure recommended by the manufacturer for nebulizer hygiene.

On the other hand, errors in therapeutic nebulization procedures are often reported in hospitals as well, being often left to the individual experience of the physician, more often of a nurse, who carries it out without shared written procedures to follow (55-58).

Choosing an inhalation drug delivery system

Some recent meta-analyses show that the clinical results for a given drug offered by different dispensers are substantially equivalent if used correctly (59, 60). Therefore in real life, when many dispensers are available for the aerosol delivery of a given drug, the choice must be made according to the clinical situation (60); when there are still more possibilities, the choice should be based on the preference of the user or caregiver and whether a good technique may be achieved for use. No strict methods for defining which dispensing system is preferable are shown, but many experts are convinced that inhalers are easier to use than nebulizers (48, 61).

It has been observed that the treatment of patients with asthma or COPD, especially if moderate or serious, requires the regular administration of several drugs via inhalation. This has led, over the last few years, to the widespread use of drugs with long-lasting action and dispensers containing a combination of several drugs rather than individual drugs taken sequentially, thereby reducing the number of daily administrations and increasing treatment compliance, especially if treatment is long-term (62).

The availability of preconstituted combinations of drugs in one dispenser can increase the clinical efficacy of the treatment, as well as encourage compliance.

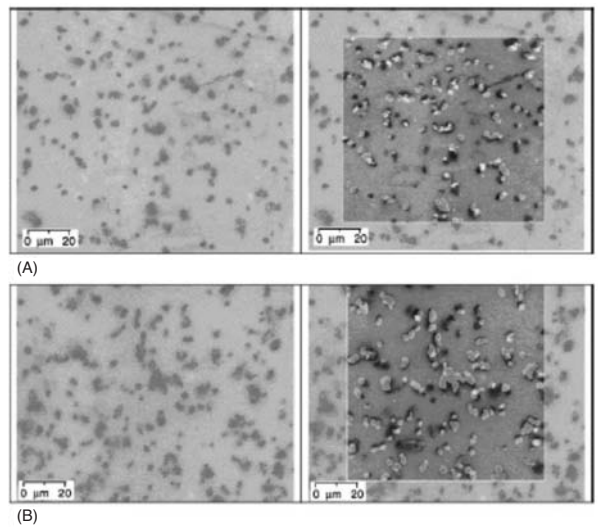

Figure 4. Raman laser analysis of the preconstituted combination fluticasone-salmeterol (A) and of the extemporaneous combination (B) of the two drugs. The molecules emitted by the dispenser may be visually differentiated by virtue of their different colours: fluticasone and salmeterol may be identified by their colors, which are green and red respectively, whereas the yellow identifies the united particles of fluticasone and salmeterol (63)

A study based on a spectroscopic analysis carried out with the "Raman" laser technique, has in fact shown that the particles of the corticosteroid fluticasone propionate and the bronchodilator salmeterol emitted from the same spray dispenser, tend to closely adhere to each other at a significantly greater degree than is observed when they are administered separately (Fig. 4) (63).

This physical phenomenon seems to enable them to be deposited together in the airways, with an increased opportunity for synergic interaction in that site. This would explain the greater efficacy in respiratory parameters observed with the preconstituted combination fluticasone+salmeterol than with the two drugs administered separately (64).

Indications in the guidelines

With regards to the method of administration, the GINA guidelines for asthma management recom-

mend the use of inhaler therapy, which enables the user to achieve maximum efficacy with a minimum amount of adverse effects. It is recommended that younger children use the spray canister with the aid of a spacer and a face mask, in order to optimize lung deposition of the drug.

Powder dispensers may also be used by cooperating children, aged over 6 years. Nebulizers are indicated as an alternative administration method which presents a series of disadvantages: inconvenient, cumbersome, lengthy administration, need for maintenance, no precision for inhaled dose. The GOLD guidelines for the treatment of COPD do not recommend the use of nebulizers for regular maintenance therapy.

The ERS guidelines (65) on nebulizer use specify that:

- the most common application for nebulizer therapy is for the administration of short acting bronchodilators in patients with asthma and COPD.
- Nebulizer therapy may be necessary in adult patients who are unable to use an inhaler, despite the appropriate spacer (Evidence C).
- Nebulization continues to be used in hospitals because it is easier for healthcare staff to administer and requires less cooperation by the patient.
- Nebulized corticosteroids used to treat flare-ups in adult and pediatric asthmatic patients, should be replaced by therapeutically equivalent doses of the drug administered more easily with a metered dose inhaler, with a spacer if necessary; in fact there is no evidence of any advantages obtained with nebulizers, which are more expensive and time-consuming (Evidence C).

However, the most recent guidelines on asthma and COPD (1, 2) indicate that the most important requirement is that the chosen dispenser is used properly. This suggestion, based on the evidence that errors in use and maintenance are frequently made in all inhalation type drug dispensers, requires all medical staff to pay more attention to the educational aspects of inhalation therapy (28, 66).

It has recently been shown that, such as with any type of inhaler, simply reading the package instructions does not appear to be sufficient to ensure proper use of the device, whereas only regular training with practical examples, provided by the medical staff, represents an efficient strategy for reducing errors in inhalation technique (Fig. 5) (67), such as regularly checking the patient's use of the dispenser (and correcting any errors) at each follow-up visit (Table 8).

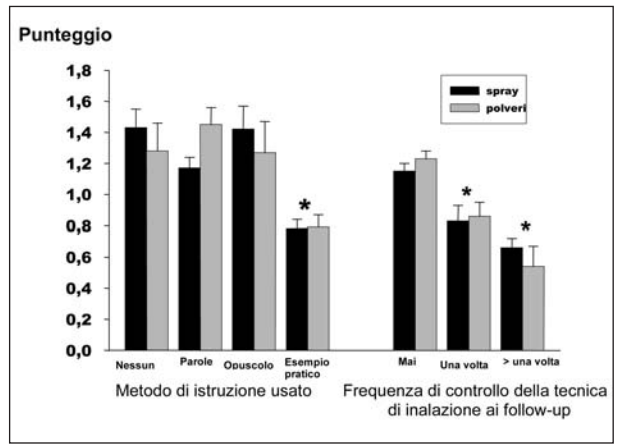

Figure 5. Effects of different types of training for the correct inhalation technique at the time of the first prescription and when checked at routine follow-up visits. Modified from (67).

Other healthcare professionals should be involved, such as pharmacists (68-71), nurses (72) or physiotherapists (73), who in countries other than Italy have shown that they can play a significant training role in this process of teaching patients to self-manage their inhalation therapy.

Conclusions

It appears clear that inhalation therapy is a complex treatment in which: a) the dispenser system is of huge importance in ensuring the efficacy of the therapy; b) in comparison with the nebulizers, the metered-dose inhalers are less cumbersome and more convenient to use at home, by stable patients; however, they can be used incorrectly, and this can jeopardize the clinical efficacy of the treatment; c) the best way to optimize inhaler technique and adherence to the prescribed treatment consists in accurate, repeated healthcare training on how and when to use the inhalers, rather than simply "changing" the dispenser.

Table 8. Requirements for teaching the correct inhalation technique

Work out a procedure for teaching each patient who comes for an appointment or to the pneumology department how to use the inhalers prescribed to them; alternatively never ask others to carry out this training.
When the patient is prescribed an inhaler, give him/her a thorough explanation, without rushing, of each step of the inhalation technique, in a quiet room; then carry out the whole inhalation procedure yourself using a placebo inhaler, without stopping, in front of the patient.
Ask the patient to bring his/her inhaler to each follow-up visit and observe him/her while he/she uses it.
Correct any errors made by the patient until he/she has acquired the correct technique; if he/she does not manage to use it correctly, change the inhaler.
Ask the patient if he/she feels comfortable using the prescribed inhaler or whether he/she prefers a different one. If necessary go back to the previous inhaler or explain why it was replaced.
Inform the patient that the inhaler is to be used whenever necessary, if prescribed, and must always be kept in a pocket or handbag so that it is always immediately available when needed.
Tell the patient to write down the date he/she started using the inhaler; to note down the times he/she uses the inhaler, if it does not have a dose-counter; to check the expiration date regularly; never to leave the inhaler where it is too cold, or in a hot, damp environment.
If a spacer chamber has been prescribed, check how the patient uses it, whether he/she uses it regularly and whether the maintenance is carried out according to the method and times indicated in the manufacturer's information sheet, or as suggested by the physician.

In conclusion, we should like to emphasize that inhalation therapy is a complex procedure and a common effort is required in terms of education between physicians, users, and manufacturers of drugs and aerosol dispensers, in order to achieve the best results. In particular, the patient must acquire the conviction that without correct use and maintenance of the aerosol dispensing system, the clinical result will be reduced or eliminated; manufacturers should promote teaching activities aimed at the best use of therapeutic aerosols, by regularly providing the prescribing centers with placebo inhalers; the physicians and all medical staff who see patients using aerosol therapy should teach the "correct use" of the dispensers and regularly check that this has been learned and continues to be put into practice.

References

1. National Institute of Health. Global Initiative for Asthma. Global strategy for asthma management and prevention: NHLBI/WHO Workshop Report Bethesda, MD: National Institutes of Health 2002. Publication N° 02-3659. http://www.nhlbi.nih.gov/guidelines/asthma/asthmagdln.htm. Ultimo accesso 01 Maggio 2007.
2. National Institute of Health, National Heart, Lung and Blood Insitute. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease- updated 2003. Bethesda: National Institutes of Health, National Heart, Lung and Blood Institute. http://www.nhlbi.nih.gov/health/prof/lung/copd/copd_wksp.htm. Ultimo accesso 01 Maggio 2007.
3. Celli BR, MacNee W. ATS/ERS Task Force: standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932-46.
4. Gandevia B. Historical review of the use of parasympatholitic agents in the treatment of respiratory disorders. *Postgrad Med J* 1975; 51 (Suppl. 17): 13-20.
5. Muers MF. Overview of nebuliser treatment. *Thorax* 1997; 52 Suppl. 2: S25-S30.
6. Freedman T. Medihaler therapy for bronchial asthma: a new type of aerosol therapy. *Postgrad Med* 1956; 20: 667-73.
7. Bell JH, Hartley PS, Cox JS. Dry powder aerosols. I A new powder inhalation device. *J Pharm Sci* 1971; 60: 1559-63.
8. Baum EA, Bryant AM. The development and laboratory testing of a novel breath actuated pressurized inhaler. *J Aerosol Med* 1988; 1: 219-20.
9. O'Callaghan C, Wright P. The metered-dose inhaler. In Bisgaard H, O'Callaghan C, Smaldone GC, Eds. Drug delivery to the lung. Marcel Dekker Inc., New York 2002; Chapter 10: 337-70.
10. Melani AS, Aiolfi S, Canessa P, Cinti C, Neri M, per il gruppo Educazionale AIPO. Caratteristiche degli inalatori pressurizzati e di polveri: revisione della letteratura. Parte I. Rassegna di Patologia dell'Apparato Respiratorio 2003; 18: 46-61.

11. Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998; 12: 1346-53.
12. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Lung deposition of hydrofuoroalkane-134a beclomethasone is greater than the of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone: a cross-over study in healthy volunteers. *Chest* 2002; 122: 510-6.
13. Menzies D, Nair A, Hopkinson P, McFarlane L, Lipworth BJ. Differential anti-inflammatory effects of large and small particle size inhaled corticosteroids in asthma. *Allergy* 2007; 62: 661-7.
14. June DS, Schultz RK, Miller NC. A conceptual model for the development of pressurized metered-dose hydrofluroalkane-based inhalation aerosols. *Pharm Technol* 1994; 18: 40-52.
15. Brambilla G, Ganderton D, Garzia R, Lewis D, Meakin B, Ventura P. Modulation of aerosol clouds produced by pressurised inhalation aerosols. *Int J Pharm* 1999; 186: 53-61.
16. Gabrio BJ, Stein SW, Velasquez DJ. A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers. *Int J Pharm* 1999; 186: 3-12.
17. Janssens HM, de Jongste JC, Hop WC, Tiddens HA. Extra-fine particles improve lung delivery of inhaled steroids in infants: a study in an upper airway model. *Chest* 2003; 123: 2083-8.
18. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Influence of particle size and patient dosing technique on lung deposition of HFA-beclomethasone from a metered dose inhaler. *J Aerosol Med* 2005; 18: 379-85.
19. Melani AS, Rossi M. Valutazione sulla modalità di impiego di Autohaler, un inalatore semplice da usare. Rassegna di Patologia dell'Apparato Respiratorio 2004; 19: 76-80.
20. Sheth K, Wasserman RL, Lincourt WR, Locantore NW, Carranza-Rosenzweig J, Crim C. Fluticasone propionate/salmeterol hydrofluoroalkane via metered-dose inhaler with integrated dose counter: performance and patient satisfaction. *Int J Clin Pract* 2006; 60: 1218-24.
21. Ogren RA, Baldwin JL, Simon RA. How patients determine when to replace their metered-dose inhalers. *Ann Allergy Asthma Immunol* 1995; 75 part 1: 485-9.
22. Rubin BK, Durotoye L. How do patients determine that their metered-dose is empty? *Chest* 2004; 126: 1134-7.
23. Sander N, Fusco-Walkert SJ, Harder JM, Chipps BE. Dose counting and the use of pressurized metered-dose inhalers: running on empty. *Ann Allergy Asthma Immunol* 2006; 97: 34-8.
24. Cyr TD, Graham SJ, Li RKY, Lovering EG. Low first-spray drug content in albuterol metered-dose inhalers. *Pharm Res* 1991; 8: 658-60.
25. Melani AS, Neri M, per la Sezione Educazionale del Gruppo di Studio Attività Educazionali Preventive. Uso degli inalatori pressurizzati e di polveri: revisione critica della letteratura. *Rassegna di Patologia dell'Apparato Respiratorio* 2001: 16: 43-64.
26. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J* 2002; 19: 246-51.
27. Crompton GK. Problems patients have using pressurized aerosol inhalers. *Eur J Respir Dis* 1982; 63 (Suppl. 119): 101-4.
28. Crompton GW, Barnes PJ, Broeders M, Corrigan C, Corbetta L, Dekhujizen R, Dubus, JC, Magna A, Massone F, Sanhiz J, Viejo JL, Voshaar AT for the Aerosol Drug Management Improvement Team. The need to improve inhalation technique in Europe: a report from the Aerosol Drug Management Improvement Team. *Respir Med* 2006; 100: 1479-94.
29. Melani AS, Zanchetta D, Barbato N, Sestini P, Cinti C, Canessa PA, Aiolfi S, Neri M, for the Associazione Italiana Pneumologi Ospedalieri Educational Group. Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. *Ann Allergy Asthma Immunol* 2004; 93: 439-46.
30. Bisgaard H, Anhoj J, Wildhaber JH. Spacer devices. In Bisgaard H, O'Callaghan C, Smaldone GC, Eds. Drug delivery to the lung. Marcel Dekker Inc., New York 2002; Chapter 12: 389-420.
31. Baldini G, Pifferi M, Visonà G, Rizzini P, Fasolo A, a nome di un Gruppo di studio Italiano. Preferenze del bambino asmatico nell'uso degli inalatori: un confronto fra Diskus e Turbohaler. *Riv Ital Broncopneumol Pediatr* 1998; 3: 210-7.
32. Mitchell JP, Coppolo DC, Nagel MW. Electrostatics and inhaled medications: influence on delivery via pressurized metered-dose inhalers and add-on devices. *Respir Care* 2007; 52: 283-300.
33. Brindley A, Sumby BS, Smith IJ, Prime D, Haywood PA, Grant AC. Design, manufacture and dose consistency of the Serevent Diskus inhaler. *Pharm Technol Eur* 1995; 7: 14-22.
34. Wetterlin K. Turbuhaler: a new powder inhaler for administration of drugs to the airways. *Pharm Res* 1988; 5: 506-8.
35. Olsson B. The revision of the Inhalandia monograph of the European Pharmacopoeia. *J Aerosol Med* 1998; Suppl. 1: 13-16S.
36. Meakin BJ, Cainey J, Woodcock PM. Effect of exposure to humidity on terbutaline delivery from Turbuhaler dry powder inhalation devices. *Eur Respir J* 1993; 6: 760-1.
37. Fuller R. The Diskus: a new multi-dose powder device. Efficacy and comparison with Turbuhaler. *J Aerosol Med* 1995; 8: S11-S17.
38. Borgstrom L, Asking L, Lipniunas P. An in vivo and in vitro comparison of two powder inhalers following storage at hot/humid conditions. *J Aerosol Med* 2005; 18: 304-10.
39. Robbins RA, Thomas AR, Proctor LM, Hoyt JC, Hayden JM. Heat decreases formoterol delivery. *Chest* 2005; 128: 4036-40.
40. Clark AR, Hollingworth AM. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers: implications for in vitro testing. *J Aerosol Med* 1993; 6: 99-110.

41. Srichana T, Martin GP, Marriott C. Dry powder inhalers: the influence of device resistance and powder formulation on drug and lactose deposition in vitro. *Eur J Pharm Sci* 1998; 7: 73-80.
42. Tarsin WY, Pearson SB, Assi KH, Chrystyn H. Emitted dose estimates from Seretide Diskus ans Symbicort Turbuhaler following inhalation by severe asthmatics. *Int J Phar* 2006; 316: 131-7.
43. Melani AS, Pirrelli P, Del Donno M, Bonavia M, Canessa C, Giacomelli C, Cilenti V, Martucci P, Sena A, Grande G, Cappiello V, Aliani M, Neri M, on behalf of the Associazione Italiana Pneumologi Ospedalieri Educational Group GENEBU Project. Equipment and drugs used for home nebulizer therapy in Italy. *Monaldi Arch Chest Di*s 2002; 57: 331-6.
44. Melani AS, Cinti C. per il Gruppo Educazionale AIPO. Nebulizzatori per aerosolterapia a fini pneumologici in Italia: indagine conoscitiva e considerazioni critiche. *Rassegna Patologia Apparato Respiratorio* 2004; 19: 193-205.
45. Melani AS, Balcke A, Schushnig U, Stempfle P, Jahn D, Keller M. Un confronto fra alcuni nebulizzatori per aerosolterapia disponibili in commercio. *Rassegna Patologia Apparato Respiratorio* 2006; 21: 61-7.
46. Bracci LS, Aiolfi S, Melani AS, per il Gruppo Educazionale AIPO. Aerosolterapia con nebulizzatori a fini pneumologici. Revisione critica della letteratura: aspetti tecnici. *Rassegna Patologia Apparato Respiratorio* 2005; 20: 64-83.
47. Bracci LS, Canessa PA, Melani AS, per il Gruppo Educazionale AIPO. Aerosolterapia con nebulizzatori a fini pneumologici. Revisione critica della letteratura: aspetti clinici. Parte I. *Rassegna Patologia Apparato Respiratorio* 2005; 20: 232-245.
48. British Thoracic Society Nebuliser Project Group. Current best practice for nebuliser treatment. *Thorax* 1997; 52 Suppl. 2: S1-24.
49. Bracci LS, Canessa PA, Melani AS, per il Gruppo Educazionale AIPO. Aerosolterapia con nebulizzatori a fini pneumologici. Revisione critica della letteratura: aspetti clinici. Parte II. *Rassegna Patologia Apparato Respiratorio* 2006; 21: 28-45.
50. Kamin W, Schwabe A, Kramer I. Inhalation solutions – which ones are allowed to be mixed? Physico-chemical compatibility of drug solutions in nebulisers. *J Cyst Fibros* 2006; 5: 205-13.
51. McKenzie JE, Cruz Rivera M. Compatibility of budesonide inhalation suspension with four nebulizing solutions. *Ann Pharmacother* 2004; 38: 967-72.
52. DiBerardino, Scaglione F. Mixing albuterol and corticosteroid is not additive. *Allergy* 1999; 54: 1012-13.
53. Berlinski A, Waldrep JC. Nebulized drug admixtures: effect on aerosol characteristics and albuterol output. *J Aerosol Med* 2006; 19: 484-90.
54. Melani AS, Sestini P, Aiolfi S, Barbato N, Canessa P, DeAngelis G, Zanchetta D, DeTullio R, Cinti C, Neri M, on behalf of the Associazione Italiana Pneumologi Ospedalieri (AIPO) Educational Group. Home nebulizer use and maintenance in Italy. *Eur Respir J* 2001; 18: 758-63.
55. Craig IR, Riley MR, Cooke NJ. Prescribing of nebulized bronchodilators- can we change bad habits? *Respir Med* 1989; 83: 333-4.
56. Caldwell NA, Milroy R, McCabe J, Banham SW, Moran F. An audit of nebulisation technique in a major teaching hospital: scope for improvement. *Pharm J* 1991; 247: 706-8.
57. Khoo SM, Lim TK. Prescribing and administration of nebulized bronchodilators: a prospective audit in a university hospital. *Respirology* 2003; 8: 205-7.
58. Rau JL, Restrepo RD. Nebulized bronchodilator formulations: unit-dose or multiple-dose? *Respir Care* 2003; 48: 926-39.
59. Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, Douglas G, Muers M, Smith D, White J. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technology Assessment* 2001; 5: 1-139.
60. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand P, Rau JL, Smaldone GC, Guyatt G. Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* 2005; 127: 335-71.
61. O'Donohue WJ Jr, Chair and the National Association for Medical Direction of Respiratory care (NAMDRC) Consensus Group. Guidelines for the use of nebulizers in the home and at domiciliary sites. Report of a Consensus Conference. *Chest* 1996; 109: 814-20.
62. Rau JL. Determinants of patient adherence to an aerosol regimen. *Respir Care* 2005; 50: 1346-1356.
63. Theophilus A, Moore A, Prime D, Rossomanno S, Whitcher B, Chrystyn H. Co-deposition of salmeterol and fluticasone propionate by a combination inhaler. *Int J Pharm* 2006 Apr 26;313(1-2):14-22.
64. Nelson HS, Kenneth RC, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol from a single inhaler versus separate inhalers. *JACI* 2003; 112 (1): 29-36.
65. ERS Task Force: European Respiratory Society Guidelines on the use of nebulizers. *ERJ* 2001; 18: 228-42.
66. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. *Respir Care* 2005; 50: 1360-74.
67. Sestini P, Cappiello V, Aliani M, Martucci P, Sena A, Vaghi A, Canessa PA, Neri M, Melani AS, on behalf of the Associazione Italiana Pneumologi Ospedalieri (AIPO) Educational Group. Prescription bias and factors associated to improper uso of inhalers. *J Aerosol Med* 2006; 19:127-36.
68. Cain WT, Cable G, Oppenheimer JJ. The ability of the community pharmacist to learn the proper actuation techniques of inhaler devices. *J Allergy Clin Immunol* 2001; 108: 918-20.
69. Mickle TR, Self TH, Farr GE, Bess DT, Tsiu SJ, Caldwell FL. Evaluation of pharmacists' practice in patient education when dispensing a metered-dose inhaler. *Ann Pharmacother* 1990; 24: 927-30.
70. Kesten S, Zive K, Chapman KR. Pharmacist knowledge

and ability to use inhaled medications delivery systems. *Chest* 1993; 104: 1737-42.
71. Hawksworth GM, James L, Chrystyn H. Characterization of the inspiratory manoeuvre when asthmatics inhale through a Turbohaler pre- and post-counselling in a community pharmacy. *Respir Med* 2000; 94: 501-4.
72. Self TH, Kelso TM, Arheart KL, Morgan JH, Meduri GU. Nurses' performance of inhalation technique with metered dose inhaler plus spacer device. *Ann Pharmacother* 1993; 27: 185-7.
73. Song WS, Mullon J, Regan NA, Roth BJ. Instruction of hospitalized patients by respiratory therapists on metered-dose inhaler use leads to decrease in patient errors. *Respir Care* 2005; 50: 1040-45.

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