

CHALLENGES OF INHALER USE IN THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The mainstay of the pharmacological management of asthma and chronic obstructive pulmonary disease (COPD) is the use of inhaled drugs. This route enables drugs to be delivered to the site of their action, minimising the risk of adverse effects caused by systemic absorption. Drugs that can be administered by the inhaled route include the most commonly prescribed drugs for asthma and COPD, namely short and long-acting β_2 agonists and anticholinergic drugs and corticosteroids. There are two main types of inhalers: pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). pMDIs were introduced in the mid-20th century. The active drug is held in suspension or solution in a canister with a propellant. Proper use of pMDIs requires the patient to apply a series of techniques correctly: i) fire the device, releasing the aerosol very shortly after the initiation of inspiration; ii) inspire slowly and deeply; and iii) hold their breath. Many patients find this procedure difficult. Modifications and add-ons include breath-activated pMDIs and spacers and valved holding chambers; these help to obviate some of the problems with pMDIs. DPIs are breath-activated devices. Following priming, which is different for each device, the aerosol is generated by the patient taking a deep, rapid inspiration. This de-aggregates the powdered drug from its carrier. A prolonged breath-hold is then required. Many studies have shown that errors that may impair the effective delivery of the drug to the lungs, including critical errors, are very common with both pMDIs and DPIs. Such inhaler misuse has been shown to be associated with poorer symptom control and more frequent emergency department attendances. Errors in the use of inhalers can be a consequence of device-related factors, patient-related factors, and health professional-related factors. Minimising inhaler misuse requires the prescribing physician to choose, in cooperation with the patient, the most suitable device for the individual patient. Education and training with subsequent monitoring and re-training are thereafter crucial. There remains a need for more user-friendly devices, which provide constant doses of the active agent, in addition to built-in dose counters and patient feedback.

Keywords: Asthma, chronic obstructive pulmonary disease (COPD), inhaler, pressurised metered dose inhaler (pMDI), dry powder inhaler (DPI), adherence.

INTRODUCTION

Asthma is a chronic respiratory disorder characterised by airway inflammation and hyperresponsiveness, which causes airway obstruction that is reversible in the majority of cases.¹ Asthma results in episodic respiratory symptoms of cough, wheeze, chest tightness,

shortness of breath, and sputum production. The aetiology of asthma remains poorly understood, although genetic and environmental factors are both important. Asthma is commonly classified as atopic or non-atopic. The former term implies a causative role of Type 1 hypersensitivity. It affects both children and adults and is common in both sexes. It is estimated that asthma currently affects

300 million people worldwide, and is responsible for 1 in every 250 deaths.² There are marked variations in its prevalence between countries, and it is generally more common in developed countries. However, it is increasing in frequency in underdeveloped countries. The economic costs of asthma are considerable: over a decade ago, the total direct cost to the USA was estimated to be \$1.5 billion.³

The aim of asthma management is disease control. Complete control has been defined as follows: no daytime symptoms; no night-time awakening due to asthma; no need for rescue medication; no asthma attacks; no limitations on activity including exercise; normal lung function; and minimal side effects from medication.⁴ International and national guidelines on asthma management stress that inhaled drugs are the mainstay of treatment.⁴⁻⁶ Drugs that can be administered by this route include short and long-acting β_2 agonists and anticholinergic drugs, corticosteroids, and mast cell stabilisers. A stepwise approach to asthma management is recommended, starting treatment at the step most appropriate to the initial severity of the patient's condition, achieving early control, and maintaining control by stepping treatment up and down as appropriate. For mild intermittent asthma, an inhaled short-acting β_2 -agonist is commonly used. If regular preventative therapy is required, evidence suggests that inhaled corticosteroids are likely to be the most effective. In younger children, however, oral drugs such as leukotriene receptor antagonists may be preferred. A rational next step would be to add a long-acting β_2 agonist. The use of mast cell stabilisers and anticholinergic drugs has generally diminished, but may be useful in individual patients.

Chronic obstructive pulmonary disease (COPD) is not a single disease, but rather a heterogeneous collection of disorders whose key defining feature is post-bronchodilator limitation of expiratory airflow by comparison with lung volume.⁷ This is associated with chronic inflammation, with mucous plugging, fibrosis, and parenchymal destruction. Airflow is usually measured by the forced expiratory volume in 1 second (FEV_1) and lung volume as the forced vital capacity (FVC). To some extent, the definition is arbitrary and the chosen cut-off for $FEV_1:FVC$ has varied. Both FEV_1 and FVC decrease with age, but FEV_1 does so more rapidly, adding a further complexity to the definition. However, a ratio of <0.7 is most usually used as the cut-off.⁷ The two principal disorders constituting COPD

are chronic bronchitis and emphysema. There are a number of conditions in which there may be a restriction in expiratory airflow, but which are usually excluded from the definition of COPD. These include cystic fibrosis and bronchiectasis. COPD is the third leading cause of mortality worldwide. Cigarette smoking is the leading cause of COPD but it can occur in those who have never smoked. Cough, mucus production, chest tightness, and shortness of breath on exertion are the main symptoms of COPD, a further characteristic feature of which is the occurrence of exacerbations, often infective.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), established in 1998, has played a leading role in championing improved management of COPD.⁸ As with asthma, mainstays of drug treatment are short and long-acting β_2 agonists, anticholinergic drugs, and inhaled corticosteroids. Given that a degree of irreversibility of airflow is, by definition, present in COPD, β_2 agonist bronchodilators have obvious limitations and there is therefore a greater potential role for anticholinergic drugs.⁹ The aim of management is the relief of present symptoms and reduction in the risk of future adverse health events.^{10,11} A common system is to divide patients into four groups depending on the severity of current symptoms and the severity of future risks. Short-acting β_2 agonists are recommended for current symptom relief in all groups. Such treatment may suffice for those patients with low-risk and mild symptoms (Group A). For those with low-risk but more severe symptoms a long-acting bronchodilator is recommended (Group B). For those assessed as being at increased risk of future events, a corticosteroid in combination with a long-acting β_2 agonist or a long-acting anticholinergic drug are recommended because these reduce exacerbation rates and improve lung function and health status (Group C and Group D).

Inhaled therapy for asthma and COPD seeks to deliver drugs rapidly and directly into the airways (the site of the pathology). This allows high local drug concentrations to be achieved, whilst limiting systemic toxicity. Inhaled therapy can be given via a nebuliser, a pressurised metered dose inhaler (pMDI), or a dry powder inhaler (DPI). Only the latter two of these will be considered in this review.

PRESSURISED METERED DOSE INHALERS

Introduced in the mid-20th century, pMDIs remain the most commonly prescribed device for delivering inhaled therapy. They deliver a fixed medication dose from a pressurised canister containing a mixture of the drug and a propellant. Previously, the propellant was a chlorofluorocarbon, but these have now been replaced by hydrofluoroalkanes. The drug may be held either in a suspension or in a solution. After the aerosol is released, the propellant evaporates and deposits the active drug along the respiratory tract.

The steps that must be followed when using a pMDI are as follows: the cap is removed from the inhaler mouthpiece; the inhaler is shaken (this is not necessary if the drug is in solution); the inhaler is held upright; the patient breathes out maximally; the inhaler mouthpiece is placed between the patient's lips and teeth, with the tongue out of the way of the mouthpiece; the patient starts breathing, and just after fires the inhaler; the patient continues to breathe in slowly and as deeply as possible; the inhaler is removed from the mouth whilst the breath is held for as long as possible (preferably at least 10 seconds); finally, the patient breathes out slowly.¹² Slow inhalation reduces the quantity of drug deposited in the oropharynx, maximal inspiration facilitates peripheral deposition of the drug, and holding the breath for as long as possible facilitates sedimentation and diffusion by Brownian motion. If the device is fired too early (prior to the onset of inspiration) or too late then delivery of the drug to the lungs is markedly reduced. There is much room for error and many patients find using pMDIs difficult.

A number of modifications and add-ons to pMDIs have been developed. With breath-activated pMDIs, airflow at the onset of inspiration triggers release of the inhaler. This overcomes the difficulty many patients have coordinating firing of pMDIs with the onset of inspiration. Spacers (valved holding chambers [VHCs]) were developed to help overcome the same problem.¹³ The aerosol is captured in a reservoir before the patient breathes it in. However, the patient is still required to inspire slowly and then hold their breath. Used appropriately, deposition of the drug is reduced in the oropharynx and increased in the lungs. The valve in VHCs prevents expiration into the aerosol. Even with these add-ons, drug delivery to the

lungs can still be significantly impaired if there is a long delay between releasing the aerosol and inhalation. Moreover, plastic devices accumulate electrostatic charges, which attracts aerosol particles to the walls of the chamber. Regular cleaning with a household detergent is necessary to counter this. It is not possible for the patient to know when a pMDI is nearly empty, other than by keeping a careful count of the number of doses used.

DRY POWDER INHALERS

DPIs are breath-activated devices. The drug is either housed in a rigid gelatine capsule that is then placed in a holder, or delivery chamber, and released by piercing, or multiple doses are enclosed in a reservoir or in a foil strip. The steps that must be adhered to when using a DPI are as follows: the mouthpiece cover is removed; the patient sits upright or stands; the inhaler is primed according to the instructions for the specific device; the patient exhales completely, away from the mouthpiece; the mouthpiece is placed between the teeth and the lips are closed around it; the patient inhales as forcibly as possible, trying to breath faster as the breath progresses; the inhaler is removed from the mouth; the breath is held for as long as possible; the patient breathes out slowly; and the cover is replaced.¹² The turbulent flow generated by inspiration is crucial for de-aggregating the drug from its carrier. The subsequent size of the aerosol particles varies with the acceleration and the velocity of the airflow achieved during inspiration. In turn, this affects where the particles are deposited in the respiratory tract. Some DPIs have a low internal resistance and require the patient to generate a high inspiratory flow. Others have a higher internal resistance and the respiratory flow required to generate sufficient turbulence is lower. Devices are available to measure the inspiratory flow rates that individual patients can generate.¹⁴

Whilst DPIs overcome some of the problems of pMDIs, they introduce new ones: some patients, particularly young children and the very old, are unable to generate sufficient inspiratory flow to effectively use DPIs; humidity and environmental temperature changes can affect the de-aggregation of the drug and carrier; and if the patient exhales into the device prior to inhaling, the powder will be dispersed and will tend to clog the tube. These factors differ according to the individual device.

Therefore, it is simplistic to attempt to choose an inhaler based solely on patient age. However, in general the majority of children over 5 years of age can generate sufficient inspiratory pressures to use DPIs.¹⁵

PROBLEMS WITH EXISTING DEVICES

The Extent of Inhaler Misuse

The incorrect use of pMDIs and DPIs is common.¹⁶ Giraud and Roche¹⁷ devised a system for primary care physicians to assess the adequacy of patients' inhalation techniques for pMDIs. They subdivided failings in any of the steps involved in correct use of the device as either omissions or errors. Omissions include failing to remove the cap, not holding the inhaler correctly, the device not being actuated at the beginning of inspiration, no slow inspiratory flow, >1 puff, and no 5-second breath-holding period at the end of inspiration. Errors included forced expiration, no expiration, inspiration through the nose, actuation of the device at the end of inspiration, and no inspiration. Patients were classified as 'misusers' if at least one error or omission was made. A total of 4,078 adults were assessed and 71% were classified as misusers, with 47% of these showing evidence of coordination difficulties. Molimard and colleagues¹⁸ studied a mixed group of 3,811 adult patients with asthma and COPD who were using a variety of pMDIs and DPIs. GPs were asked to assess the adequacy of the patient inhaler techniques using both generic and device-specific criteria. Errors were considered 'critical' if they could have substantially reduced drug delivery to the lungs. Overall, 76% of patients made errors with pMDIs and these were considered critical in 28%. Depending on the device, at least one error was made with DPIs in 49–55% of patients, which were considered critical in 11–32% of patients.

A subsequent literature review of data from various European studies confirmed very high error rates in the use of inhalers.¹⁹ This review concluded that up to 50% of patients in Europe were not using inhalers correctly. In addition, up to 40% of children were not using spacer devices correctly. Lavorini and colleagues²⁰ evaluated published data on the errors made with DPIs in patients with asthma and COPD. They found that, depending on the type of inhaler and method of assessment, between 4–94% of patients did not use their inhalers correctly. Although different studies have found marked differences in error rates between

different types of inhalers, these are not consistent between studies; a device which performed well in one study may perform poorly in another.^{12,20,21}

The problem of poor inhaler technique is not confined to primary care. A multicentre, cross-sectional, observational study of 1,664 adult patients with asthma and COPD attending chest clinics in Italy found evidence of critical mistakes, ranging from 12% of patients for MDIs up to 44% of patients using one particular type of DPI (the Turbohaler).²²

The Consequences of Inhaler Misuse

There is accumulating evidence that misuse of inhalers contributes significantly to poor symptom control. Giraud and Roche¹⁷ correlated their findings regarding patient's inhalation techniques with asthma instability scores based upon: daytime respiratory symptoms; asthma-related nocturnal waking; exercise-induced asthma; β_2 agonist use; serious exacerbations; and global assessment by the GP of the evolution of the patient's condition during the previous month. They found asthma to be less stable in pMDI misusers than in correct users, with asthma instability scores of 3.93 versus 2.86, respectively ($p < 0.001$).

In an Italian study performed in asthma and COPD patients, the finding of critical errors in inhaler technique was associated with an increased risk of hospitalisation ($p = 0.001$), emergency department visits ($p < 0.001$), use of antibiotics ($p < 0.001$), and courses of oral corticosteroids ($p < 0.001$).²² Al-Jahdali et al.²³ reported a cross-sectional study of all patients ($n = 450$) visiting an emergency department with asthma over a 9-month period in two major hospitals in Saudi Arabia. The inhaler technique of each patient was assessed using a checklist, and asthma control over the preceding month was assessed by administering an Arabic version of the asthma control test (ACT).²⁴ There was evidence of improper device use in 45% of patients. This was associated with uncontrolled asthma ACT scores ($p = 0.001$) and three or more emergency department visits ($p = 0.0497$). The authors concluded that improper asthma device use was associated with poor asthma control and more frequent emergency department visits.

The Reasons for Inhaler Misuse

Sanchis and colleagues¹² undertook a literature review of the errors observed whilst using pMDIs and DPIs. Only 34% of patients were assessed as

having an overall adequate technique when using pMDIs. Errors were made in every step of the process, with particularly frequent errors involving the need to shake the device, the coordination of firing the device with the start of inspiration, continuing to breathe slowly and deeply after firing the device, and breath holding. With regards to DPIs, the errors made varied significantly depending on the type of DPI. However, common errors occurred in relation to priming the devices, breathing out and away, inspiring forcefully and deeply, and breath holding. Overall, up to 19% of patients were judged to have made critical errors.

A useful method of considering why there is such a high rate of inhaler misuse is to assess those that are device-related, patient-related, and healthcare professional-related.¹⁶ The extraordinary range of available devices is testament to manufacturers' attempts to overcome the problems with existing devices; unfortunately, this factor has become part of the problem itself. Devices differ according to whether the aerosol is generated actively or passively, whether it is held in suspension, solution, or as a dry powder, whether they contain single or multiple doses, are disposable or refillable, and what a 'standard dose' is. A degree of manual dexterity and hand-breathing coordination is required to successfully use all inhalers. Patients differ in the value they attach to their inhalers, the importance they perceive their inhalers to have in controlling their symptoms, and in the consequent quality of their lives. In some cultures, the use of inhaled medication may be considered impolite in public. Some pMDIs contain

alcohol that may not be acceptable for religious reasons. The importance of factors such as device aesthetics, medication taste, and ease of cleaning vary greatly between patients. The incorrect use of inhalers has been shown to be significantly associated with irregular clinic attendance and a lack of patient education.²³ Healthcare professionals including physicians, specialist nurses, and pharmacists play a crucial role in choosing which inhaler to prescribe/dispense, and in training patients to use their inhalers correctly, and yet studies have shown that only a minority of such professionals can themselves use inhalers correctly.²⁵

Three patient groups deserve special mention: young children, the elderly, and those with learning and/or physical disabilities. Young children may not have the necessary cognitive and motor skills to use inhalers. Even if they do, their maximal inspiratory flow rates may be less than that required for breath-activated DPIs.¹⁶ For these reasons, pMDIs with spacers, face masks, and oral medications are often used in the very young. Licensing issues may also be important to consider because some potentially suitable devices may not have a paediatric licence.

Manual dexterity, hand-breathing coordination, and cognitive functions may all decline with old age and therefore simpler-to-use and larger devices may help to overcome consequent difficulties. For those with disabilities, problems arising from cognitive and memory problems, physical problems, and visual-spatial difficulties may alone or in combination lead to difficulties using inhalers.

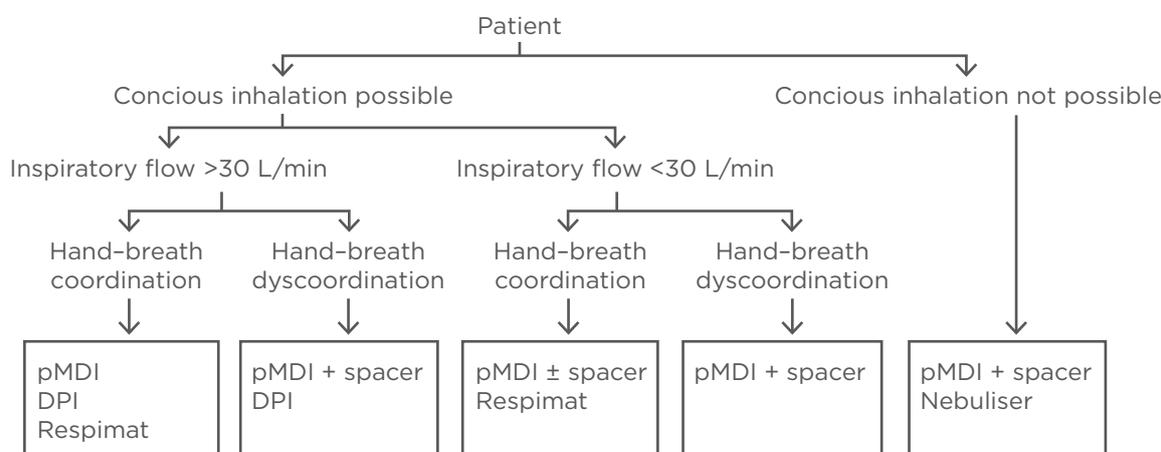


Figure 1: A clinical algorithm that utilises the patient's respiratory flow rate and hand-breath coordination to help physicians choose an appropriate inhaler device.²⁹

DPI: dry powder inhaler; pMDI: pressurised metered dose inhaler.



Figure 2: Non-commercial and commercial training tools for inhaler devices.³³

Overcoming Inhaler Misuse

Overcoming problems with the use of inhalers starts with the prescriber choosing the most appropriate device for the individual patient.^{26,27} This must be followed by educating and training the patient in the use of the device (alongside more general asthma and COPD education and training). A system of monitoring should be in place, along with ongoing training, in order to maintain an appropriate level of patient skill.

The key issues to consider when choosing an inhaler is the device(s) with which the patient is already familiar or already using, the patient's preference, their ability to use the device correctly, the availability of devices that can deliver the desired drug, the convenience and portability of available devices, and the familiarity of the physician with potential devices.²⁸ The opposing breathing techniques needed to correctly use pMDIs and DPIs means that their concurrent use has obvious disadvantages and is discouraged. In practice, however, the use of short-acting β_2 agonists given via pMDIs is so common that many patients do use both types of device concurrently. Algorithms can be of assistance to help physicians make the most appropriate choice of inhaler device (Figure 1).²⁹

Educating patients and the families of patients with asthma and COPD about the rationale for the use of inhaled medication, and the problems and pitfalls associated with it, should help them to

understand why good inhaler-use technique is likely to be critical to achieving the shared physician-patient goals. This is distinct from training in the use of an individual device. It is important to identify who is responsible for device training. This may be the prescribing physician, a specialist nurse, or the dispensing pharmacist. Whoever is responsible must themselves have appropriate knowledge and skills. It has been demonstrated that training sessions for healthcare professionals are effective.^{30,31} Focussed interventions with patients teaching inhaler technique have been shown to be effective in reducing inhaler errors. Physical demonstration of how to use a specific inhaler is more effective than only providing written or verbal instructions.³² The technique should be explained, demonstrated, and then the patient's technique physically checked. The use of checklists and objective tools to assess correct inhalation patterns for specific devices can be helpful (Figure 2).³³ Training sessions can be provided individually or in groups, and group sessions at school for children may be useful. Inhaler technique tends to deteriorate quickly and regular repetition of training is essential.³⁴ In addition, patients should have access to written or electronic information to which they can refer between training sessions, particularly if the use of inhaled medication is on an intermittent basis.

If patients continue to show poor technique with a particular device despite appropriate education and training then switching to a different device whose properties are likely to overcome the

patient's specific difficulties should be made. In this regard, the Respimat® Soft Mist™ inhaler is a relatively new type of device that, in a similar manner to pMDIs, delivers drugs as an aerosol. Rather than using a propellant, however, the aerosol is generated mechanically by forcing a metered dose of the drug in solution through a uniquely designed nozzle, which produces a fine mist. The advantages claimed over conventional devices include ease of use with regards to coordination and the improved deposition of the drug in the lungs rather than in the upper airways.³⁵

Finally, inhaler devices require intermittent cleaning. Patients should be reminded of the importance of this and asked to follow the manufacturer's instructions. Failure to do so may result in a loss in the efficacy of drug delivery.³⁶

THE FUTURE

The 'ideal' inhaler has yet to be designed. Empirically, it would be user-friendly, not require priming or coordination between triggering and inhalation, would provide dose consistency independent of environmental conditions and inhalation manoeuvres, have a dose counter that was based on actual inhalations rather than manipulations, would provide the patient with a clear but not unpleasant perception of drug delivery, and would provide feedback to confirm that a dose had been inhaled, that the technique

used was correct, and provide a reminder about adherence.²¹

Manufacturers are exploring the use of new technologies, both intrinsic and extrinsic to the devices, in order to improve compliance. The extrinsic technologies include, for example, phone apps. Some of these may significantly add to the costs of treating asthma, at least in the short term.

CONCLUSIONS

Despite the seemingly alarming statistics regarding how often inhalers are used incorrectly, the fact that they are the preferred method of delivering drugs to treat patients with asthma and COPD is in itself evidence of their overall efficacy. The requirements of any two patients are hardly ever exactly the same. Therefore, it is unlikely that one 'ideal' inhaler would suit all patients. The physician treating patients with asthma or COPD has the luxury of a wide choice of inhalers that, if used correctly, can deliver the active drug to where it is required, minimising the risk of adverse effects. To optimise therapy, however, the choice of which inhaler to prescribe needs to be an informed one and made carefully in collaboration with the patient. Specific training in the use of the device is essential, as is ongoing monitoring and re-training. Clinicians should be willing to switch patients to alternative inhalers if, despite all of this, the patient is unable to use the device correctly.

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