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REVIEW

The ADMIT series – Issues in Inhalation Therapy. 4) How to choose inhaler devices for the treatment of COPD

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Abstract

For patients with COPD, inhalation is the preferred route of administration of respiratory drugs for both maintenance and acute treatment. Numerous inhaler types and devices have been developed, each with their own particularities, advantages and disadvantages. Nevertheless, published COPD management guidelines pay little attention to the optimal choice of inhaler devices for COPD patients. Although efficacy and safety are the primary factors determining the choice of an inhaler device, randomised controlled trials (RCTs) directly comparing the efficacy and safety of different inhalers in COPD patients are scarce. Systematic reviews on this subject failed to find significant differences between devices for any of the clinical outcomes studied. When selecting a device for the delivery of inhaled drugs in 'real life' patients with COPD, other factors should be considered. These include availability and affordability of the inhaled drugs and inhaler devices, the uniformity of inhaler devices when several drugs are to be inhaled, the ability of patients to handle correctly the selected device – in particular taking into account the advanced age of the average COPD patient, and finally the patient's preference. The prescribing clinician's task is to provide comprehensive instructions for correct handling of the device and to review regularly the patient's inhalation technique.

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Contents

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Introduction

When treating respiratory disorders such as chronic obstructive pulmonary disease (COPD), the inhaled route is the preferred route for administering respiratory drugs. Reasons for this include both efficacy and safety. Indeed, although COPD patients – in particular those with severe disease – may require higher inhaled doses to penetrate the lung than patients with asthma, inhalation (as opposed to systemic administration) allows drug dosages to be kept relatively low while remaining sufficiently effective because the drug is delivered directly to the airways, the site of action. Consequently, systemic availability – and therefore the potential for extra-pulmonary side effects – is minimised (see Figure 1) due to the improved topical/systemic ratio afforded by the inhaled route which is safer and better tolerated than oral administration. Furthermore, efficacious and safe administration of drugs may enhance patient adherence to the prescribed treatment.

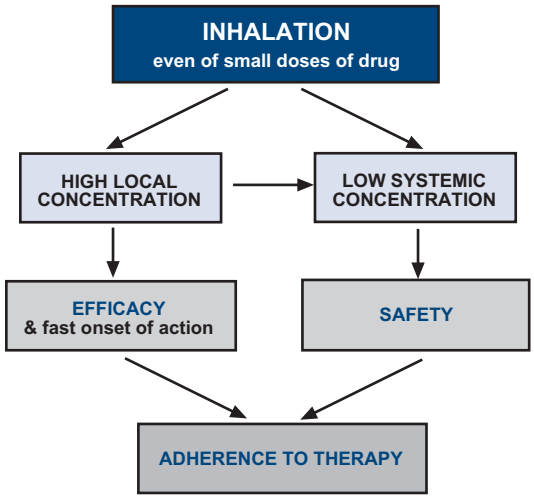
Therefore, the development of an easy-to-use inhaler device that delivers effectively the aerosolized or dry powder drug to the lungs, is as important as the development of an efficacious and safe drug itself.

Although every national and international COPD management guideline acknowledges that inhalation is the preferred route of administration of respiratory drugs,[1-7] these same guidelines hardly address the characteristics of the inhaler devices needed to deliver these medicines. In the recently published updated GOLD executive summary,[7] inhaler devices and technique are not mentioned as a 'key point' in the guideline section 'Component 3: manage stable COPD'. However, the authors do deserve some credit for mentioning inhaler devices in two sections. On page 541 they state: "When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique are essential". The same message is repeated on the next page, with the addition of the following: "The choice of inhaler device will depend on availability, cost, the prescribing physician, and the skills and ability of the patient. Patients with COPD will have more problems in effective coordination and find it harder to use a simple pressurised Metered Dose Inhaler (pMDI) than do healthy volunteers or younger patients with asthma. It is essential to ensure that inhaler technique is correct and to recheck this at each visit". Although relatively sparse given the total content, this attention to inhaler devices and their handling is a great step forward in comparison to earlier guidelines – from GOLD and others – which paid even less attention to this important aspect of COPD patient treatment.

Many patients derive incomplete benefit from their inhaled medication because they do not use the devices correctly or they fail to maintain correct inhaler technique. This is clearly one of the major limitations to treatment. In order to deal with it there is a clear need for specific inhaler technique education, and training of patients and physicians alike.[8]

The aim of this article therefore is to review the literature dealing specifically with inhaler devices in COPD, and to extract from it the factors that appear of key importance in choosing the most appropriate inhaler device for the individual COPD patient.

Figure 1. Advantages of the inhaled route of drug administration.



Available and frequently used inhaled drugs in COPD

Bronchodilators are considered the cornerstone of pharmacologic treatment of COPD, while glucocorticosteroids and mucolytics – in particular those also displaying antioxidant properties – play a more restricted role (see Table 1).

Among the inhaled bronchodilators, both β_2-adrenergic receptor agonists and anticholinergic agents are commonly used in COPD. Indeed (and in contrast to asthma) increased parasympathetic (vagal) bronchomotor tone appears to be a major reversible component of airflow limitation in COPD patients.[9-12]

Besides, being more effective than (or at least as effective as) inhaled β_2-adrenergic receptor agonists, inhaled anticholinergics are considered to be very safe. Their quaternary ammonium

Table 1. Respiratory drugs and inhaler devices for COPD.*

Drug class	pMDI	DPI	Nebuliser	Other inhaler
SAAC	√	(√)	√	-
LAAC	-	H	-	Respimat
SABA	√	N, T	√	Autohaler
LABA	√	N, A, T, D	-	-
SABA + SAAC	√	(√)	√	(Respimat)
ICS	√	N, A, T, D	√	Autohaler
ICS + LABA	√	A, T, D	-	-
Theophylline	-	-	-	-
Mucolytic / antioxidant	-	-	√	-

*: Not exhaustive list.
√: available in most European countries; (√): available in some European countries; -: not available in Europe.
H: Handihaler; N: Novolizer; T: Turbuhaler (or Turbohaler); A: Aerolizer; D: Diskus; SAAC: short-acting anticholinergic; LAAC: long-acting anticholinergic; SABA: short-acting B2-adrenergic receptor agonist; LABA: long-acting B2-adrenergic receptor agonist; ICS: inhaled corticosteroid

structure avoids gastro-intestinal absorption of the ingested fraction, and therefore their systemic availability and extra-pulmonary effects are very limited, depending solely on the fraction that is deposited in the airways. β_2-adrenergic receptor agonists on the other hand do undergo gastro-intestinal absorption, and since hepatic first-pass extraction is not complete this may lead to measurable plasma levels and extra-pulmonary side effects. In the (usually) elderly COPD population, co-morbidity – in particular, cardiovascular disease – is frequently present and has to be taken into account in the choice of inhaled drugs, especially bronchodilators.

Nevertheless, a recent meta-analysis of 17 randomised controlled trials (RCTs) enrolling 14,783 COPD patients raised some doubt on the cardiovascular safety of inhaled anticholinergics (ipratropium or tiotropium).[13] Although all-cause mortality was not different between any inhaled anticholinergic and control therapy, the composite end-point of cardiovascular death, myocardial infarction or stroke occurred significantly more frequently in the anticholinergic-treated patients than in the control patients (1.8% versus 1.2%, respectively). Critical analysis of this paper – not least noting the fact that some studies were double counted or unpublished – reveals that differences in discontinuation rates, and hence patient exposure time, were not taken into account, and that the results were heavily weighted by a single ipratropium study, a retrospective analysis of which showed that most of the cardiovascular deaths occurred in patients not using their inhalers.[14] The possible association between ipratropium and elevated risk for all-cause and cardiovascular death was also raised from the results of a recent nested case-control study,[15] and needs further study. However, contrary to the findings in Singh *et al*'s meta-analysis,[13] the recently published UPLIFT study,[16] comparing 4-years treatment with the long-acting anticholinergic tiotropium versus placebo (both on top of usual treatment) in 5993 COPD patients, showed no increased risk for cardiovascular death (risk ratio 0.73), myocardial infarction (risk ratio 0.73) nor stroke (risk ratio 0.95). When calculating from the UPLIFT data Singh *et al*'s composite end-point of cardiovascular death, myocardial infarction or stroke, this was not elevated in the tiotropium-treated patients as compared to the control group (unpublished data). These UPLIFT data confirm a previous safety analysis which pooled data from 19 RCTs including 4435 tiotropium-treated and 3384 control patients with COPD.[17] In this pooled analysis, all-cause mortality (risk ratio 0.76), cardiovascular mortality (risk ratio 0.57) and respiratory mortality (risk ratio 0.71) were not increased in the tiotropium group as compared to the control group, thus supporting the present safety profile of tiotropium.

Therefore, and as stated in the GOLD guideline,[6,7] an inhaled anticholinergic drug, in particular one with long-acting activity such as tiotropium, or a long-acting β_2-adrenergic receptor agonist (LABA) such as salmeterol or formoterol, may be considered first choice in the maintenance treatment of COPD – the next step then being to provide a combination of both in case of insufficient effectiveness.

Besides these long-acting agents, inhaled short-acting bronchodilators belonging to either the anticholinergic or β_2-adrenergic receptor agonist classes are also available. Furthermore, fixed combinations of the short-acting anticholinergic (SAAC) ipratropium bromide and a short-acting β_2-adrenergic receptor agonist (SABA), in particular fenoterol or salbutamol, can be prescribed. These combinations of short-acting drugs are used in acute situations for quick symptom relief but also as chronic maintenance therapy when long-acting agents are not available. However, for long-term maintenance treatment, long-acting inhaled bronchodilators should be preferred to short-acting ones mainly for reasons of efficacy,[11,18] convenience, and possibly improved patient adherence to prescribed maintenance therapy.[6]

Slow-release theophylline, another long-acting bronchodilator belonging to the methylxanthine class, is not available for inhalation and hence has become less utilised. Other reasons include its narrow toxic-therapeutic margins, unpredictable serum levels following oral ingestion, and interactions with many other drugs.

Whereas inhaled corticosteroids (ICS) are the mainstay of maintenance treatment in asthma, their role in COPD is more restricted. Addition of an ICS to maintenance treatment with (one or more) long-acting bronchodilators is recommended in more severe COPD patients with a forced expiratory volume in one second (FEV_1) less than 50% of the predicted value who experience frequent exacerbations.[6,7] Several placebo-controlled studies have shown that in this particular patient subpopulation,

daily treatment with an ICS can reduce exacerbation frequency,[19-24] although even this finding has been criticised recently because of supposed improper statistical techniques.[25]

Studies examining long-term treatment with the combination of an ICS and a LABA in patients with at least moderately advanced COPD[26-29] and a systematic review thereof[30] do show that this combination is more effective than placebo in terms of symptoms, lung function, health-related quality of life and exacerbation rate. When both an ICS and a LABA are prescribed, their combination in one single device is not only more convenient but probably is more effective than their administration using two separate devices. This at least has been demonstrated for the LABA salmeterol and the ICS fluticasone propionate using the Diskus® device in asthma patients.[31,32]

Available inhaler devices

A wide range of inhaler devices is available for patients with COPD, thus permitting treatment to be tailored to the individual but at the same time making it more difficult to make the correct choice for individual patients.[33,34]

In general, inhaler devices can be grouped into three categories according to the method used for drug dispersion (see Table 1 and Figure 2). The electrically-powered 'wet' nebuliser aerosolises a liquid drug solution by using compressed air or vibration of a Piezoelectric crystal. The two types of mechanically-driven pocket-sized inhalers – the pMDI (with or without a holding chamber or spacer) and the dry powder inhaler (DPI – of which many types exist) – make use of a propellant under pressure, and the patient's own inspiratory effort, respectively, to disperse the drug. From this panacea of available inhaler devices, it can also be deduced that the inhaler device fulfilling all of the requirements for the ideal device (see Table 2) has yet to be developed.

In most countries, the pMDI remains a popular and commonly used device for administration of respiratory drugs to patients with respiratory diseases. The pMDI is portable, quickly to hand and relatively inexpensive. The wet aerosol is driven by a propellant in which the active drug is dissolved or is in suspension. Because they contribute to global warming by depletion of the stratospheric ozone layer, chlorofluorocarbon (CFC) propellants have been replaced by the more environmentally-friendly hydrofluoroalkanes (HFA). Other ozone-friendly alternative inhaler devices have been developed, notably the DPIs. All these inhaler devices have advantages and disadvantages in terms of their drug delivery characteristics, reliability, consistency and ease of use.[35,36] Like CFC-driven pMDIs, the HFA-driven pMDIs require perfect co-ordination between hand actuation of the device and inhalation, a requirement many patients lack.[37,38]

Adding a spacer device (preferably a large volume one) to the pMDI, or using a breath-actuated pMDI such as the Autohaler® or Easi-Breathe® device, helps to solve the problem of hand-inhalation co-ordination and improves pulmonary drug delivery.[39] Attaching a spacer to a pMDI also filters out the larger non-respirable particles and slows down the emitted aerosol, such that pulmonary deposition increases from around 10% using a pMDI to 20% or more using a pMDI plus spacer.[40]

Another solution for the hand-inhalation co-ordination problem is achieved by using a DPI. Besides being as convenient and portable as a pMDI (without a spacer), they are also breath-actuated, i.e. they only release a dry powder aerosol of the drug with or without a lactose carrier when the patient inhales forcefully enough through it. Instances exist where patients are unable to generate sufficient inspiratory flow to guarantee adequate de-aggregation and dispersion of the dry powder particles and, hence, sufficient or sufficiently deep pulmonary deposition. Differences in internal device resistance between

Figure 2. Available inhalation systems.

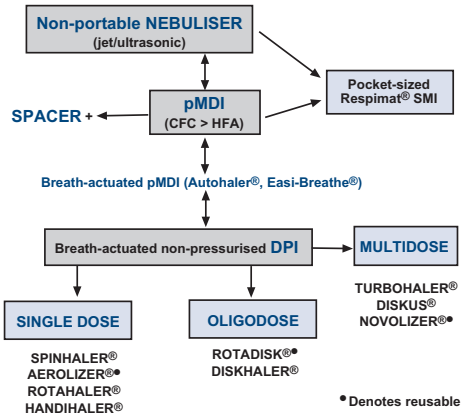


Table 2. Requirements of the 'ideal' inhalation system.

User- and environmentally-friendly: easy to use and learn ready for use or fast & easy loading portable, small, pocket-sized yet robust breath-actuated, uses only human energy control & safety features (visible; audible; dose count) pure drug; no harmful additives / carriers / propellants (CFCs) multidose uses refills
Dosing and delivery independent of: external conditions (e.g., humidity) inspiratory flow rate (low internal device resistance)
Slow release of aerosol
High respirable fine-particle fraction
High pulmonary (also peripheral) deposition
Low oropharyngeal deposition
If liquid: solution instead of suspension

Figure 3. Some of the available hand-held inhaler devices.

various DPIs will therefore affect pulmonary deposition.[41] Many different types of DPIs have been developed, some of which are shown in Figure 3. They can be subdivided according to the number of doses they contain, whether they contain preloaded doses or require loading, and whether they are reusable (Figure 2). Some of these DPIs provide the patient with several feedback mechanisms and are able to assure the patient that the dose has been delivered correctly. For example, the single-dose Aerolizer® provides visual, auditory and taste feedback, features also present in the multi-dose Novolizer®. In addition, the Novolizer® contains an inspiratory flow triggering mechanism.

Notwithstanding the wide choice of effective pocket-sized pMDIs and DPIs, and the fact that even in emergency situations equivalent bronchodilatation can be obtained using a pMDI with a large volume spacer as compared to a nebuliser,[42] nebulisation of high-dose bronchodilators (and inhaled corticosteroids) remains widely – and often inappropriately – prescribed, at least in some European countries.[43] The reasons why jet or ultrasonic nebulisers remain very popular amongst patients probably include the fact that they deliver a visible cloud of aerosolised medication and that inhalation itself is rather uncomplicated, only requiring tidal mouth breathing. Patients are also impressed by the fact that these devices are used in the hospital and therefore 'must be good'. Many healthcare providers indeed regard nebulisers as more convenient to administer inhaled drugs in emergency situations, requiring less patient education and co-operation.[42] However, because nebulisers are less effective in terms of pulmonary deposition and are more expensive, they are generally only recommended for very young and very old patients who are unable to use pocket-sized devices correctly, and in case of emergency for very breathless and panicking patients.[42,44]

The British Thoracic Society guideline for nebulised treatment recommends assessment of the response to high-dose bronchodilators inhaled using a pMDI with spacer and the intervention of a respiratory specialist before long-term nebulised treatment is prescribed.[45] Clinical situations in which home treatment with a nebuliser is preferable to that with a pMDI plus spacer have been identified as: where the COPD patient despite appropriate instruction and demonstration is judged incapable of correctly using a pMDI (or DPI) due to locomotor, visual or cognitive limitations; and where the patient's respiratory mechanics are insufficient – i.e. a vital capacity (VC) less than 1.5 times the predicted tidal volume (V_t) of 7 ml/kg body weight, an inspiratory flow rate less than 30 l/min, or a breath-holding capacity less than 4 seconds.[44] In that same consensus statement,[44] nebuliser therapy was also recommended for the small subset of patients with severe COPD who remain symptomatic despite correct use of high-dose pMDI or DPI treatment, and for COPD patients with mucus hypersecretion or mucus clearance problems, in whom the wetting action of the nebulised aerosol might facilitate mucus elimination.[46]

Other pocket-sized inhalers, belonging neither to the pMDI or DPI classes, have become available more recently or are under development. The Respimat® Soft Mist™ inhaler may be considered a hybrid of a pocket-sized, multi-dose inhaler and a 'one-shot' nebuliser, since it slowly delivers a soft mist of drug solution with aerosol characteristics that guarantee relatively high pulmonary and limited oropharyngeal deposition.[47]

Choice of inhaler devices in COPD

While the choice of drug used for treatment is reasonably straightforward for the majority of COPD patients, the choice of delivery device is less clear, particularly in view of the ever increasing, and at times confusing, number and types of devices.

The primary factors determining the choice of an inhaler device should be efficacy and safety. However, RCTs directly comparing the efficacy and safety of different inhalers in COPD patients are scarce.

The first systematic literature review of clinical effectiveness (and cost-effectiveness) of inhaler devices used in COPD (and asthma) was published in 2001.[48] Only two studies[49,50] were identified which compared in stable COPD patients the delivery of any short-acting bronchodilator using a pMDI, with or without spacer, to that of any other (at that time available) hand-held inhaler device, namely the DPIs Rotahaler®[49] or Turbuhaler®.[50] No evidence of clinical difference in β-agonist delivery was found. The same review identified 14 studies comparing the delivery of any short-acting bronchodilator using a nebuliser to that of any (at that time available) hand-held inhaler device (usually a pMDI) in stable and acute COPD. These 14 studies, all performed between 1984 and 1995, included small numbers of patients and usually only assessed acute pulmonary function responses over a period of hours in a crossover design. Again, no evidence

of treatment difference in bronchodilator delivery was found.[48]

A Cochrane Database systematic review published in 2002 comparing the ability of pMDIs versus all other (at that time) available hand-held inhaler devices to deliver bronchodilators for COPD, could only identify 14 potentially relevant studies.[51] Of these 14 studies, 11 had to be excluded for reasons of design (not RCTs), patient population (mixing asthma with COPD patients) or comparator device (comparison of two devices from the same family, such as pMDI versus pMDI or DPI versus DPI, or comparison with nebulisers). Only three crossover studies[49,50,52] with a total of only 61 stable COPD patients were retained in the review. Two of these studies compared a DPI – in particular the Rotahaler®[49] or Turbuhaler®[50] – in only 10 and 15 patients, respectively, with a pMDI and spacer, for delivery of a SABA. The third crossover trial including only 36 patients compared the effects of the SAAC ipratropium using the Respimat® Soft Mist™ inhaler to a conventional pMDI.[52] For both DPIs, none of the reported outcome measures (pulmonary function variables and adverse events) differed significantly from those obtained with the pMDI.[49,50] Using the Respimat® Soft Mist™ inhaler, ipratropium induced significantly higher increases in FEV_1 and in FVC compared to those obtained using a conventional pMDI, while no differences between these two devices were noticed for any of the other reported outcomes (adverse events, heart rate, blood pressure, QTc interval, residual volume and airway conductance).[52] The review concluded that the very small number of available studies and included patients did not allow firm conclusions to be drawn, and that further well-designed RCTs are needed to define the role of the inhaler device for the administration of bronchodilators in COPD patients.[51]

In an open, randomised, 2-way crossover, cumulative dose-response study in COPD patients, ipratropium bromide administered using a DPI was found to be equally safe and as effective as when administered using a conventional CFC-pMDI.[53] Patients expressed a preference for the breath-activated DPI, which was found to be more acceptable and easier to use than the pMDI.

Another systematic review published in 2005 included all RCTs comparing the efficacy and safety of bronchodilators as well as inhaled corticosteroids administered with all sorts of devices – pMDIs with and without spacer, various DPIs and nebulisers – in patients with either COPD or asthma.[54] Of the 131 studies that met the eligibility criteria for this review, only 59 had usable data, primarily those that assessed β_2-agonists. The conclusion of the different pooled meta-analyses was that, at the drug doses used, no significant differences between devices could be found for any of the efficacy outcomes. Adverse events were minimal and were related to the increased drug dose that was delivered. An unavoidable 'selection' bias tending to lead to equivalent results in the RCTs assessing differences in clinical efficacy and safety between different inhaler devices is that they only include patients who are able to use the studied inhaler devices correctly. When selecting a device for the delivery of inhaled bronchodilators and inhaled corticosteroids in 'real life' patients with COPD and asthma alike, factors other than efficacy and safety (as detailed in Table 3) should be considered.[54]

Table 3. Factors influencing selection of delivery device

Efficacy and safety
Availability of device and drugs
Clinical setting
Age of patient
Ability to use the selected device
Device use with multiple medications
Cost and reimbursement
Drug administration time
Convenience in both outpatient and inpatient settings
Patient preference

After reference 54.

Other relevant considerations when choosing a COPD inhaler device

In the absence of clinically relevant differences in efficacy and safety,[36] other factors or considerations (as detailed in Table 3) appear to be more relevant in determining the choice of the most appropriate device for an individual COPD patient.

Availability of inhaled drugs and inhaler devices

Not all inhaled drugs prescribed for the treatment of COPD are available in all of the different inhalers. For example, in most countries where it is on the market, the first line LAAC tiotropium can at the time of writing only be delivered via the HandiHaler® DPI (although tiotropium Respimat® Soft Mist™ inhaler is now also available in some countries).

When different drugs are available in various types of inhalers, attention should be paid to consistency of inhaler choice. There is evidence, at least in asthma patients, that the use of multiple inhaler types confuses the patient and increases the risk of errors in their use.[55] There is no reason to believe that this should not be the case in COPD patients.[35] Using the same inhaler type for the different drugs the patient has to take may enhance his/her ability to learn the correct use of the device.

Nevertheless, in some cases it may be beneficial to use different inhaler types concomitantly, thereby combining their respective advantages. In a recent parallel group study involving 126 COPD patients treated with salbutamol and ipratropium, it was found that health-related quality of life and symptom scores improved significantly more when using a combination of nebuliser treatment in the morning and at night and a pMDI in the afternoon and evening compared to using either a nebuliser or a pMDI alone four times daily.[56]

Clinical situation: acute versus chronic maintenance therapy

The degree of breathlessness determines the choice of inhaler device preferred at that time. Thus, in acute situations, the pMDI-spacer combination or nebuliser treatment is recommended, while for chronic maintenance treatment hand-held, pocket-sized pMDIs or DPIs may be preferred.

Economic constraints

When prescribing inhaled medication to COPD patients, physicians are sometimes not aware of the differences in cost or the different reimbursement rules that may exist between the various drug-device combinations.[57,58] Patients may be unable or unwilling to pay the cost of their prescribed inhalation treatment, especially the economically weak and elderly COPD patient who often already faces large medical expenditure because of multiple co-morbidities. Physicians should take into account the cost to the patient and local reimbursement rules as this may affect the patient's adherence to prescribed inhalation treatment.[59]

Patients' ability to use the prescribed inhaler correctly

Although incorrect use of inhaler devices is common and is usually due to problems with comprehension or co-ordination, evidence exists that some devices are used with fewer mistakes than others. In a study assessing the use of seven different inhaler devices in 100 patients (aged 22-88 years) with airflow obstruction,[60] performance scores – as well as patient preference – were highest for the breath-actuated pMDIs (Easi-Breathe® and Autohaler®). The DPIs Accuhaler® (aka Diskus®) and Clickhaler® ranked next, followed by another DPI (Turbuhaler®) and the pMDI plus spacer, while the pMDI without spacer ranked worst. A 'real life' observational study in 3811 patients in primary care showed that a large proportion, not to say the majority, of patients handle their inhaler device erroneously.[61] This proportion of 'misusers' was larger for the pMDI (76%) than for the breath-actuated devices studied – i.e. the Autohaler® pMDI and various DPIs (Aerolizer®, Diskus® and Turbuhaler®) – where device mishandling occurred in 49-55% of patients.[61] A general practice study including 558 patients with asthma or COPD found the type of inhaler to be the strongest independent determinant of an incorrect inhalation technique; patients using the Diskhaler® were at lower risk of making inhalation mistakes than patients using a pMDI or the other types of DPIs studied (Rotahaler®/Spinhaler®, Turbuhaler® or Cyclohaler®/Inhaler Ingelheim®).[62] Other significant determinants of incorrect inhalation technique were low emotional quality of life and being treated in a group practice.[62] In a recent multicentre observational study including 1305 patients with asthma or COPD, it was shown that inhaler misuse was common for both pMDIs and DPIs, and was essentially associated with increasing age, lower level of education and less instruction by healthcare providers.[63] Many healthcare providers, physicians and nurses alike, are themselves unfamiliar with the correct use of (all of) the currently available inhalers.[64-67] Hence, to improve the patient's ability to use inhalers correctly, formal education – not only of the patient but also of healthcare providers – is needed; i.e. we need to 'educate the educator'.[35,36,57,59,68] After teaching the correct technique there seems to be no difference in the asthma or COPD patient's ability to use DPIs or pMDIs.[48]

Apart from questionnaire-type checklists,[54,68] instrumental aids have been developed to check and subsequently correct inhalation technique for the pMDI and different DPIs. For the pMDI, the Aerosol Inhalation Monitor™ automatically checks different phases of the inhalation process and indicates whether inspiratory flow rate was optimal (ideal 30 l/min), whether co-ordination of pMDI firing with the start of inhalation was correct, and whether subsequent duration of inspiration and of breath-holding were adequate.[69]

The In-Check DIAL™ device,[70-72] through which patients inhale as if using their usual DPI, mimics the resistance of the selected DPI whilst objectively measuring (peak) inspiratory flow rate. The In-Check DIAL™ device could help in selecting the DPI appropriate for the patient and in training for optimal use of it.[73]

Some inhalers have built-in feedback mechanisms that help to check whether the device is appropriately used. Feedback includes built-in dose counters (some pMDIs, DPIs such as Novolizer®, Accuhaler®, Clickhaler® and some Turbuhalers®), or sensory aids such as visual or auditive stimuli (Novolizer®, Aerolizer®) or taste (the presence of lactose as a carrier). Other devices indicate auditorily whether the minimally required inspiratory flow was effectively generated (Autohaler® pMDI, Novolizer®). Devices using individual dose capsules (HandiHaler®, Aerolizer®) allow verification of sufficient emptying of the capsule after inhalation.

Ageing and handling of inhaler devices

COPD is a disease which becomes apparent in middle-aged current and ex-smokers and predominantly affects elderly people. Age, and in particular ageing, can affect the patient's cognitive and physical abilities (i.e. manual dexterity and visual acuity) which in turn influence the ability to handle inhaler devices correctly. Therefore, this factor should be taken into account when prescribing inhaled medicines.[74,75] Elderly patients with cognitive impairment – as demonstrated by a mini-mental test score below 23/30 or a Hodgkinson mental test score below 7/10 – are unlikely to learn and retain correct pMDI inhaler technique.[76] In patients aged 63-85 years, the rate of successful use almost doubled from 36% for a conventional pMDI to 64% using a breath-actuated pMDI.[77] When prescribing a pMDI in elderly patients, either a breath-actuated pMDI[77] or a regular pMDI in combination with a

large volume spacer should be prescribed.[5,78] Comparing these two alternatives in 423 patients aged over 70 years but with intact cognitive function, the pMDI with a large volume spacer was more frequently correctly used than a breath-actuated inhaler.[79] Although the speed of dyspnoea relief was somewhat slower than with administration of bronchodilator therapy with a nebuliser,[80] dyspnoea and lung function improved to similar extents when using a pMDI plus spacer in elderly patients aged 60 years and over during an acute exacerbation of COPD.[81]

COPD patients appear to make fewer device-handling mistakes when using a DPI than when using a pMDI.[82] Another study confirmed that elderly patients aged 75-101 years more correctly used a DPI (in this study the Turbohaler®) than a pMDI, even in combination with a large volume spacer.[83] In this study, the main reason why the pMDI plus spacer combination performed less well was that patients had difficulties assembling the pMDI with the spacer. For the same reason, this study also found that patients more often correctly used a breath-actuated pMDI (in this case the Easi-Breathe®) than the pMDI plus spacer combination,[83] in direct contradiction to Ho *et al*'s findings.[79]

In a study comparing various DPIs (Aerolizer®, Diskus®, Handihaler® and Turbohaler®) in patients with asthma or COPD, it was shown that (besides the severity of disease) age critically determined the frequency of handling errors.[84] Thus, while the error rate was 20% for patients younger than age 60 years, it doubled to 41.6% for those older than 60 years and even quadrupled to over 80% for those older than 80 years. Training by the healthcare provider more than halved the overall error rate from 53% to 23%, but in older patients ineffective use of inhalers remained high despite prior instructions.[84] In a similar comparison of the pMDI with various DPIs, older outpatients with asthma or COPD had more difficulty in using the inhalers correctly than younger patients.[85]

Therefore, although comparability between the reviewed studies is difficult, it could be concluded that when choosing between inhaler devices in elderly COPD patients with intact cognitive function, priority should be given to either a DPI, a breath-actuated pMDI, or (if correct assembling can be assured) a pMDI plus spacer. Certainly, a conventional pMDI should be avoided when these alternatives are available.

Patient's acceptability and preference

The patient should be involved in the choice of the inhaler device. Patients will only use a device that they like, feel comfortable with, and can use and trust, even when breathless and incapable of high inspiratory flow rates. The most expensive device is the one a patient cannot or doesn't use.

Differences in patients' preference for a particular inhaler device have been observed. In Lenney *et al*'s study comparing the various types of hand-held devices,[60] patients preferred the breath-actuated pMDI Easi-Breathe®, while the least popular choices were the DPI Turbuhaler® and the pMDI with spacer. The other devices studied – i.e. the pMDI, the breath-activated pMDI Autohaler® and the DPIs Clickhaler® and Accuhaler® (also known as Diskus®) – scored in between. In a study comparing two different DPIs, patients with COPD preferred the Diskus® more frequently than the Handihaler®.[86] The top three features rated as important by the patients and leading to a preference were: being quick to use when needed; overall ease of use; and having a dose counter.[86]

Although patient preference appears a valid patient-reported outcome, a review of studies on preference for inhaler devices found no significant differences in clinical outcomes between devices where measured.[87] Whether the COPD patient's preference for an inhaler device translates into greater adherence is not known, mainly because of the lack of studies assessing such an association.[88] In COPD patients, compliance rates with a pMDI decrease significantly over time.[89]

Pulmonary deposition

Total or regional lung deposition of inhaled particles and droplets may be affected by aerosol properties (in particular mass median aerodynamic diameter, MMAD), mode of inhalation (inhalation technique – in particular inspiratory flow rate or effort; relatively low for a pMDI and high for a DPI) and factors relating to the patient's age and underlying disease process, in particular airway obstruction.[90] In asthma, pulmonary effects of, or clinical response to, medications inhaled via a pMDI are related to their lung deposition.[91,92]

Provided the inhalation technique is standardised, there is little evidence that the total lung deposition of an inhaled drug will differ between healthy volunteers and patients with asthma or COPD. Some studies using 'steady state' tidal breathing technique (as would be the case when using a nebuliser) for inhalation of monodispersed, labelled particles have shown increasingly central airway deposition in association with increasingly severe airway obstruction and mucus plugging.[93,94] However, when the bronchodilator ipratropium bromide was directly labelled using the radionuclide ^{77}Br and was directly inhaled from a pMDI, its total and regional lung deposition pattern was not shown to be different between the seven normal subjects and the seven patients with chronic bronchitis (mean FEV_1 32% of predicted value) who were studied.[95]

Current inhaler devices are designed to deliver drugs optimally to the conducting airways of patients with asthma. However, COPD predominantly affects peripheral airways and lung parenchyma, which may not be optimally targeted by current inhalers. Generally an MMAD below 10 μm is required for the aerosol to be deposited sufficiently in the airways, while deposition in the most peripheral airways and alveolar region requires an even smaller MMAD below 3 μm and preferably around 1 μm. It is possible that new inhaler devices delivering smaller aerosolised particles will be more

useful for COPD patients.[96]

The LAAC tiotropium, which is registered solely for COPD treatment, is inhaled using a device that should be specifically designed for use by COPD patients – i.e. the HandiHaler® device, a breath-activated DPI. As shown by both *in vitro* studies and *in vivo* studies in COPD patients, the HandiHaler® effectively delivers small respirable particles to the lungs over a wide range of airflow limitation and at peak inspiratory flow rates as low as 20 l/min.[97] Four weeks after instruction, the HandiHaler® is used more correctly by COPD patients than a pMDI.[98] Studies are now being performed with tiotropium aqueous solution delivered via the multi-dose Respimat® Soft Mist™ inhaler. This pocket-sized, propellant-free inhaler slowly releases a wet aerosol at low speed, resulting in increased pulmonary deposition and thereby allowing dose reduction.

Conclusion

Pharmacologic treatment of COPD patients preferably utilises inhalation therapy. While the evidence on which drugs to choose for acute and maintenance treatment of COPD is available from multiple well-designed RCTs, much less evidence is available regarding the choice of the optimal delivery method and in particular the optimal delivery device. The issue is rendered particularly difficult because of the plethora of inhaler devices that have and still are being made available for prescription: nebulisers, pMDIs with or without spacers, breath-activated pMDIs and DPIs, and others. Each of these devices has different properties, advantages and disadvantages, but all of them are declared an ideal device by their manufacturers…Nebulisers are generally only recommended for patients unable to use pocket-sized devices correctly, and in case of emergencies in very breathless and panicking patients. As far as the efficacy and safety of inhaled bronchodilators is concerned, the choice between a DPI, a pMDI with spacer, or a breath-actuated pMDI appears to be of little importance, at least in patients selected for inclusion in RCTs. However, in 'real life' care for COPD patients, factors other than efficacy and safety appear to be important in the choice of the most appropriate inhaler device for the individual COPD patient. These include the availability and affordability of the inhaled drugs and inhaler devices, but also a uniform choice of the inhaler device when several drugs have to be inhaled, the patient's ability to correctly handle the device(s) selected, and – although not proven to be related to treatment adherence – it seems logical to consider the patient's preference for a device. The role of the prescribing clinician is to select the most appropriate drug-device combination for the patient carefully, taking into account these elements. However, perhaps the most important obligation for the physician is to ensure adequate and sufficient instruction for correct handling of the device(s) selected as well as regular checking of the patient's inhalation technique at each subsequent visit.

Conflict of interest declaration

Conflicts of interest for all ADMIT members are listed at the end of the first paper in this series - see Dekhuijzen *et al*. *Prim Care Resp J* 2007;**16**(6):341-8.

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