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Delivering orally inhaled medications to the older patient with COPD and/or asthma: A challenge in both device design and clinical approach

Considerations for inhaler developers and prescribing clinicians

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Introduction

The inhaled delivery of therapeutic drugs presents significant challenges to both clinician and patient, because orally inhaled products (OIPs) are relatively complex to use correctly, compared with other routes of drug administration.[1] Challenges associated with adherence to prescribed medication are therefore compounded by the possibility that the older patient (defined arbitrarily as aged 65 years or older), as well as having multi-morbidities, may lack manual dexterity due to commonly encountered diseases such as arthritis or Parkinsonism.[2,3] Furthermore, the patient may have cognitive difficulties to a varying extent, and as a result is likely to be difficult to be taught correct inhaler technique in the first place, or may likely forget whatever training was received by the prescribing clinician or pharmacist.[4] The demographics in most developed countries mean that a greater proportion of the population will be reaching older age in the next 25-50 years.[5,6] Given this background, it therefore behooves those involved in the development of new orally inhaled products to pay particular attention to the human factors associated with device use.[7,8] Furthermore, the prescribing clinician and pharmacist, whose roles are vital in the chain of events that leads to successful medication delivery, need to be aware of the key issues that should be addressed when helping the older patient use, and continue to use, their inhaler(s) correctly.[9,10] Such patients commonly have one or more chronic obstructive lung diseases, in particular asthma and chronic obstructive pulmonary disease (COPD).[11] Inhaled therapy is widely accepted as the norm for all but those with the most severe disease, in which additional therapy by other routes of administration may be needed.[12-14] This article seeks to highlight some key concerns, by examining the attributes of each of the major classes of OIPs of most relevance to the older patient. In addition, consideration is given as to how the Patient Information Leaflet, sometimes called the Instructions for Use (IFU), which is a common aspect to their handling and maintenance, can be made more user-friendly in order to support and reinforce correct inhaler use.

Overview of current therapy for obstruction lung diseases

Formulations

A patient-by-patient individualistic approach to the prescribing-of inhaled medicines for treating the two major chronic diseases involving the airways of the lungs (asthma and COPD), is not yet a practical proposition.[15] Currently, both diseases are treated by topical administration of inhaled therapeutics, as being the safest route to achieve the desired degree of efficacy (Figure 1). In the case of asthma, inhaled corticosteroids (ICS) are given as controller therapy in appropriate dosing, depending on disease severity, to reduce the underlying inflammation of the airways.[13] ICS are usually combined with a long term (LABA) or ultra-long term (ULABA) beta$_2$ adrenergic agonist in a single "combination" inhaler to mitigate bronchoconstriction, and thereby providing symptom relief. A short term beta$_2$ adrenergic agonist (SABA) is also often provided in a separate inhaler as "rescue" medication for rapid relief of symptoms associated with bronchoconstriction, when felt necessary by the patient. The therapy for COPD is somewhat different, but still topical in nature. Here, an anticholinergic drug (antimuscarinic agonist) is the mainstay of therapy to treat the underlying inflammatory disease.[14] Short-acting antimuscarinic agonists (SAMAs) have been the traditional therapy; these medications are often augmented with a SABA in a combination product for symptom

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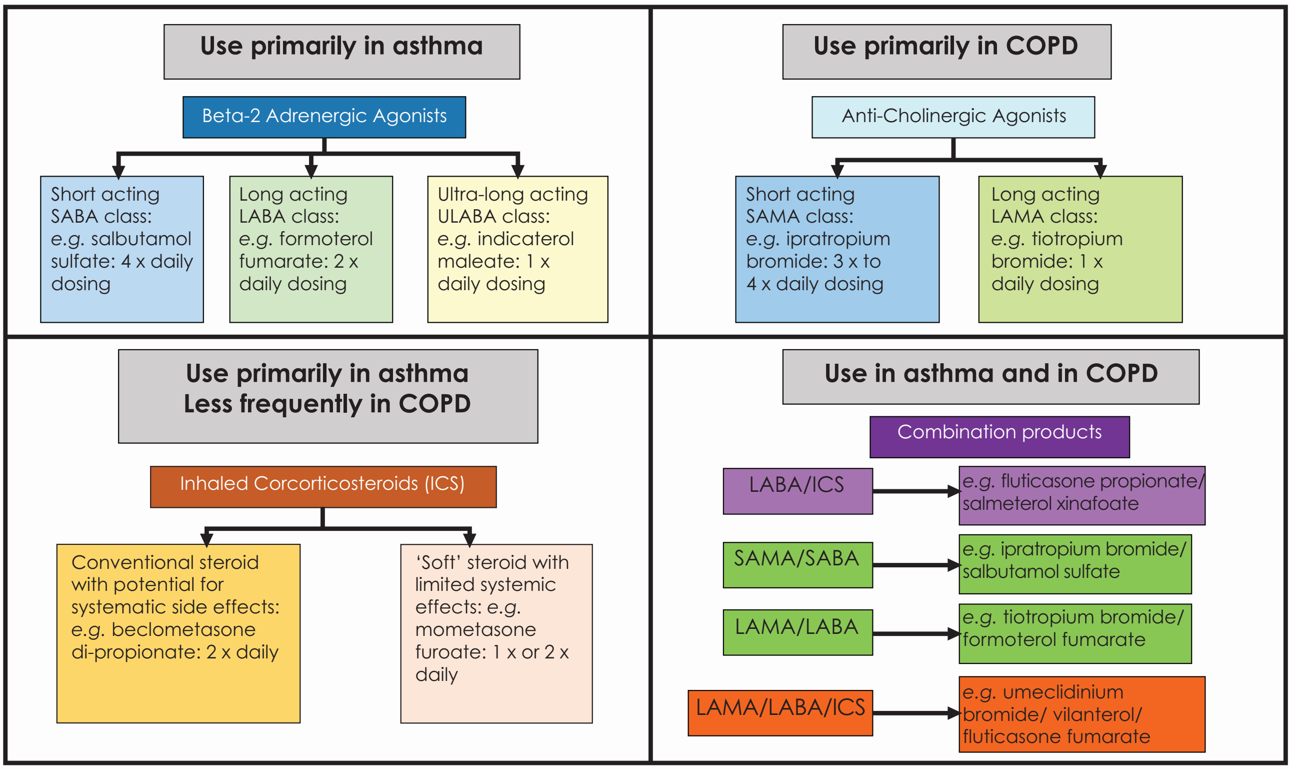
Figure 1

Therapies associated with asthma, COPD and asthma combined with COPD



relief. These days, however, the anticholinergic is likely to be long acting in nature (LAMA), and augmented with a LABA. The use of ICS is controversial in the treatment of COPD where an asthmatic (reversible bronchoconstrictive) component is not present.[16] However, there is a school of thought that many patients presenting with COPD symptoms also have an asthmatic component to their condition, so that therapy by ICS/LABA may be prescribed in a precautionary way to address both conditions simultaneously.[12] Recently, triple combination therapy in a single inhaler has become possible with ICS/LAMA/LABA medications for these patients. Combination therapies have the advantage pertinent to the older patient, that only a single inhaler device is needed to manage the disease(s) under treatment.[17]

Devices

The main classes of devices for oral inhalation are:

a) the pressurized metered dose inhaler (pMDI), with or without valved holding chamber (VHC) add-on device to mitigate medication loss associated with imperfect patient coordination of inhalation with pMDI actuation;

b) the dry powder inhaler (DPI), which may contain the powdered formulation in either a reservoir or as a single dose (capsule or pre-packaged blister-based) arrangement;

c) the soft mist inhaler (SMI), of which the Respimat® device (Boehringer Ingelheim, Germany) is the sole representative;

d) the liquid droplet nebulizer, where the drug product(s) is either dissolved in aqueous solution or prepared as an aqueous suspension.

Pneumatically-operated nebulizers are still widely used either in the hospital environment where compressed air at high pressure (50 psig) is the norm, or in the home environment where lower pressure table-top or portable air compressors are available. The simplest devices deliver the medication continuously at a fixed rate. More advanced pneumatic nebulizers make use of the additional air flow generated during the inhalation portion of each breathing cycle (air entrainment) to augment the delivery rate of medication. The most advanced devices in this category contain a storage device to retain the aerosolized medication during exhalation, or are purely breath-actuated, delivering medication only when the patient inhales. Breath-actuated nebulizers (BANs) conserve medication if the patient removes the mouthpiece temporarily, possibly to converse with a neighbor or caregiver. They also limit contamination of the local environment with the aerosolized medication droplets. More recently, electronic nebulizers, beginning with ultrasonic, followed by vibrating mesh/membrane designs, have become popular because they are efficient and have less medication wastage, therefore offering the potential for shorter treatment times.[18] However, they are more expensive, since they contain electronic as well as mechanical components.

Inhaler suitability for the older patient

The wide array of inhaler choices provides an opportu-

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Table 1

The Major Classes of Inhalers for Oral Administration of Inhaled Formulations and Their Suitability for the Older Patient

Inhaler Class	pMDI alone	pMDI + VHC	DPI	SMI	Nebulizer
Suitability for the older patient	√	√√√	√	√√	√√√
Suitability via a caregiver	√√	√√√ (with face-mask)	√	√√	√√√ (with face-mask)

√ = less suitable; √√ = suitable; √√√ = more suitable
pMDI = pressurized metered dose inhaler
VHC = valved holding chamber
DPI = dry powder inhaler
SMI = soft mist inhaler
Nebulizer could be pneumatic jet/vibrating mesh/membrane/ultrasonic

nity for the prescribing clinician to personalize treatment to better meet the needs and aptitudes of the patient.[19] Yet this complexity can also increase confusion, both with respect to device selection as well as proper administration of inhaled therapies. The degree of suitability of these devices for the older patient or caregiver by inhaler class is compared in Table 1.

Several considerations have led to the choices made in Table 1:

1. Many older users cannot coordinate the onset of inhalation with actuation of a pMDI-based product;[4] the sudden hiss associated with propellant expansion may startle the patient to exhale instead of inhaling;

2. VHCs conserve the aerosol containing the medication for several seconds after pMDI actuation; even if the patient exhales, the inhalation valve prevents exhaled air from entering the chamber and dispersing the aerosol;[20]

3. VHCs and nebulizers can be supplied with a facemask, as well as a mouthpiece, for use by the patient with limited manual dexterity and/or cognition;

4. DPIs, in general, require a significant inhalation effort to disperse the powder into an aerosol cloud having the optimum particle size distribution for deposition at receptors located at the airways of the lungs;[21] many older patents, especially those with emphysema associated with severe COPD, may be incapable of such a maneuver;[10]

5. The SMI is relatively simple to operate and delivers its medication as a low-velocity cloud (hence the name "soft mist inhaler");[22] however, without a VHC used with the SMI to capture the mist, an older patient may still exhale at the critical moment, thereby dispersing the aerosol;

6. Though relatively slow delivery devices, nebulizers can provide the widest variety of treatment options[23] (though not triple combination therapy at the present time), and are readily set up in the home environment; cleaning and maintenance may, however, be a challenge, even with the electronic nebulization systems.[18]

Regardless of the class of OIP prescribed, if patients are prescribed more than one different device type, it is important to note that the risk of failure to use both devices correctly increases.[24,25] This result is likely caused by the increased difficulty experienced in remembering which operating procedures apply to which inhaler.

Separate or in-built aids for the older patient

A few stand-alone aids are already available to improve the ability of the older patient to achieve optimum therapy with pMDI, DPI and SMI products, where correct use demands more attention by the patient than when receiving therapy by nebulizer. For example, the Lever-Haler® device (Birdsong Medical Inc., Cleveland, OH, US) provides additional mechanical advantage so that actuation of a press-and-breathe pMDI is made possible for the patient with limited finger and thumb movement in the hands. Add-on dose counters are also available for use with pMDIs not having this feature already integral to the inhaler itself. There will likely always be a market for such aids, particularly those that cannot be readily incorporated into the inhaler design, or are useful for only a minority of the total patient population receiving therapy via a particular inhaler device.

However, in the context of assisting the older patient, the challenge to developers of future products is to integrate enabling features into existing products, so that they assist in both the process of preparing the inhaler for use, and subsequently actuating it correctly. An excellent example of this approach has been the development of the breath-actuated pMDI (for example, the Maxair™ Autohaler™, 3M Drug Delivery Systems, St. Paul, MN, US). This product illustrates how the need to provide mechanical effort in order to actuate the device is eliminated by virtue of building in technology that causes the inflow of air when the patient starts inhaling to trip an in-built mechanism, thereby triggering actuation of the pMDI. All the patient has to do beforehand is to move a small, clearly color-coded lever located on top of the device to the vertical "ready-to-actuate" position. The caregiver can also readily perform this task for a patient with severe hand movement and/or cognitive ability.

The VHC is an example of an aid that by itself helps assure delivery of the fine particle component of the inhaled medication from press-and-breathe pMDIs, while retaining the coarser particulate that has no beneficial therapeutic value when it is delivered to the oropharynx, and which can result in adverse side effects with certain formulations (e.g., dysphonia and oral candidiasis with ICS).[20] However, VHCs can be, and have been improved from the basic aerosol holding chamber

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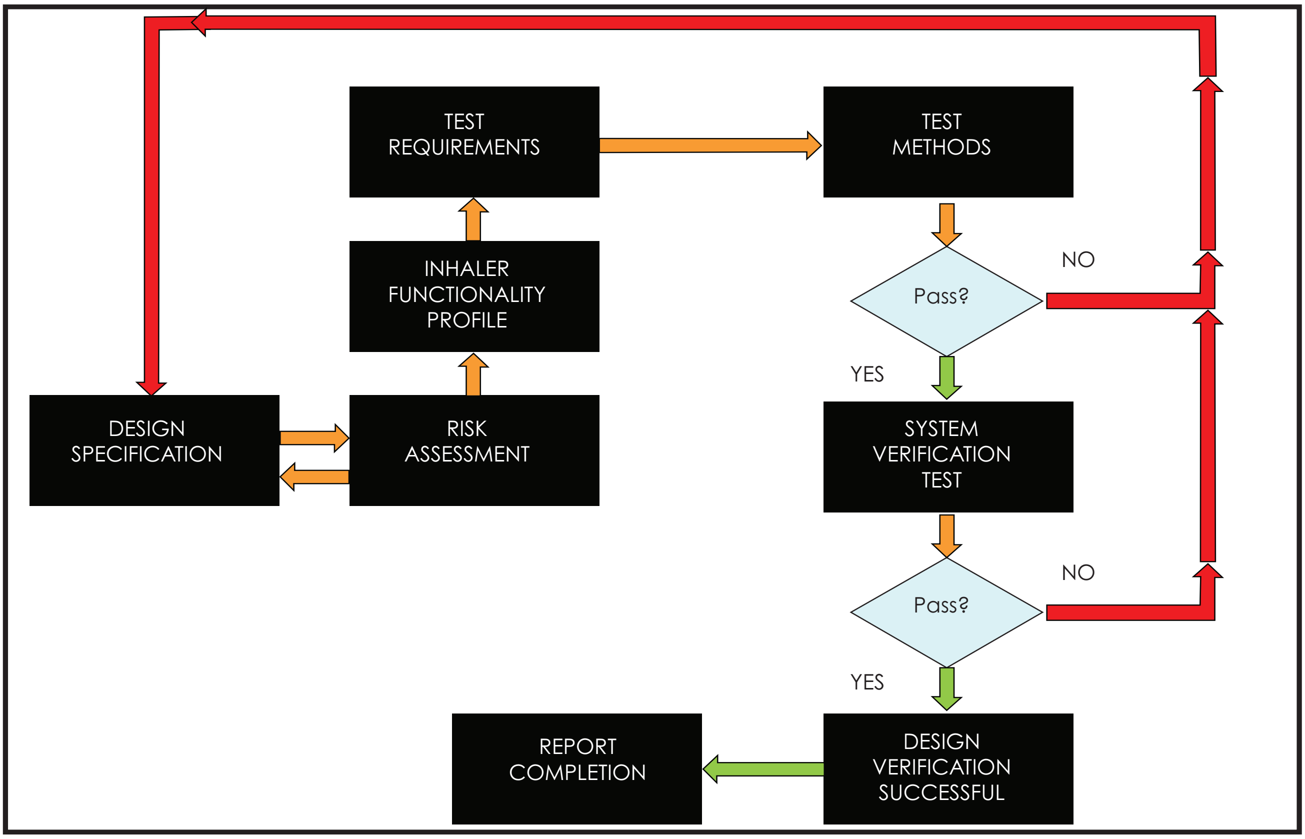
Figure 2

OIP device design process as identified in ISO 20072: 2009



concept to incorporate in-built features that add value especially for the older user. For example, the use of transparent electrostatic-charge-dissipative materials, rather than conductive metal, in construction enables a caregiver to see the aerosol cloud as it is created, providing valuable feedback that the inhaler has been operated in an effective manner, as well as providing the primary function of mitigating medication losses due to internal wall deposition of the intrinsically-charged particles emitted from the inhaler.[26] The incorporation of an indicator linked to the movement of the inhalation valve, which opens when the patient begins inhaling, is a further example of in-built enabling technology. Each member of the AeroChamber Plus® VHC family (Trudell Medical International, London, Canada) has this feature).[29] As the user breathes, the movement of the flow visualization indicator can be observed by a caregiver for the older patient. Thus, he or she can see when the patient has finished exhaling, and time inhaler actuation correctly to coincide with the start of the next inhalation. This feature is also particularly useful if the patient interface is a facemask, since once the propellant has expanded following actuation, any leak between facemask and face will result in ambient air ingress to the space between facemask and mouth/nose, rather than provide a suction force to open the valve, therefore allowing the aerosolized medication to be inhaled.[27]

A further example of an in-built patient aid, on this occasion linked with a BAN, is the green-colored button located on top of the AeroEclipse-II® inhaler (Trudell Medical International, London, Canada). This button moves downwards as the patient inhales, actuating the device, returning to its up-position once inhalation has been completed.[28] This feature could be used as a training aid for a more cognitively-aware older patient to strive for a slower and deeper inhalation during therapy, as well as providing caregiver feedback that medication is being delivered to the user with limited cognitive ability.

Inhaler device design and human factors assessment

Two recent developments have aided the process of developing OIPs for different patient needs. Firstly, in 2009, the International Standards Organization (ISO) produced a standard, ISO 20072, entitled: Aerosol drug delivery device design verification.[29] This document contains a useful road-map defining an iterative design verification process as a series of steps, beginning with a risk assessment in which the sponsor identifies potential vulnerabilities of the design, then tests for robustness of the chosen design before making improvements and repeating the cycle (Figure 2). It is at this early stage in the development of the inhaler, that considerations pertinent to the special needs of the older patient should be given.

The second development came two years later when the US Food and Drug Administration (FDA) issued a draft guidance document entitled “Applying Human Factors

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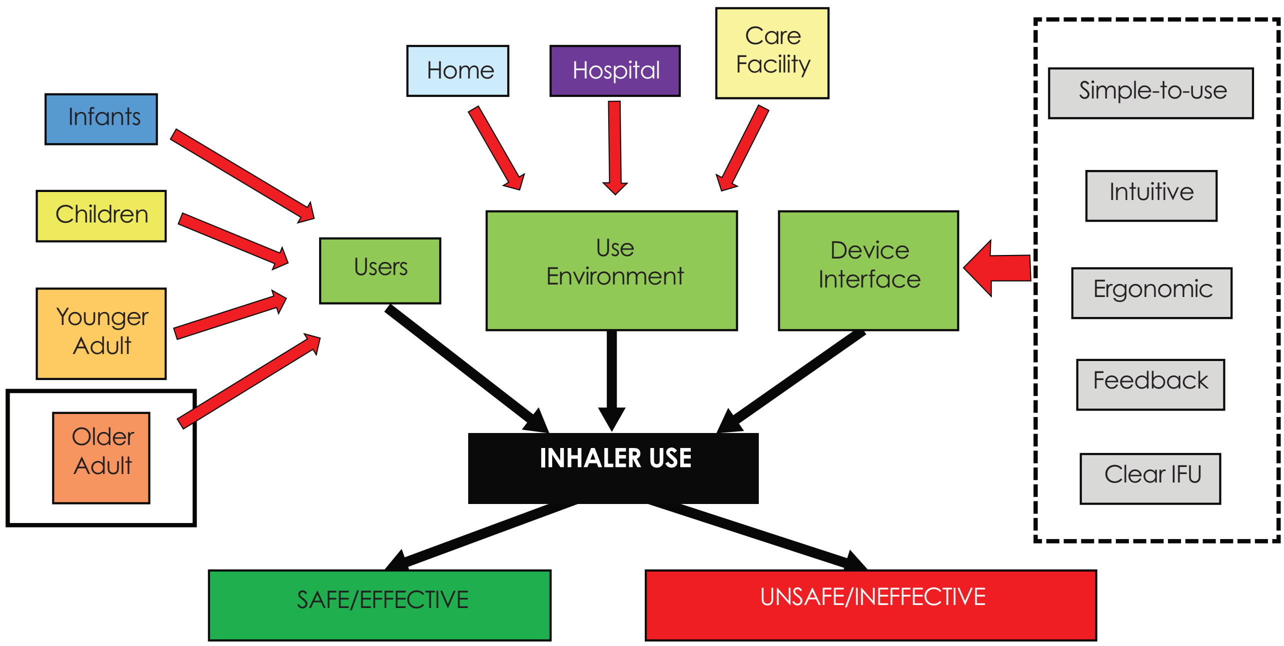
Figure 3

Adaptation of US FDA perspective on Human Factors Analysis in Medical Device Development, Focusing on the Needs of the Older Patient



and Usability Engineering to Optimize Medical Device Design."[30] Though aimed at the designers of all types of medical devices, there is the clear mandate for the OIP developer to consult and involve the eventual users in the process of bringing the inhaler from initial concept to the marketplace, as an ergonomic device for its intended population of users (Figure 3).

This process may be as simple as a usability study. It may also involve more complex interactions with patient groups reflecting key user categories, in particular age ranges, in order to differentiate between needs specific to sub-populations such as the older patient with significant limitations in ability to use inhalers. Such studies should also consider the likelihood that such patients may be receiving their therapy via a caregiver who may also be inexperienced with inhaler use.

The inhaler developer can greatly assist the prescribing clinician, pharmacist, patient and caregiver by providing Instructions for Use (IFU) written in clear language, understandable by persons with limited formal education.[31] The text should be in a large-enough font to be readable by those with mild-to-moderate visual impairment, common in the older patient.[32] Since the IFU is often discarded, carefully designed pictograms illustrating correct use are helpful on the device itself, where this is possible. If this if not possible, pictograms should be a key component of the IFU because they are easier, in general, to interpret than text. However, it is important to avoid the use of non-standard icons, in the interest of ease of rapid interpretation of information that will be key to successful operation and maintenance of the inhaler and related equipment. Finally, it should be noted that the use of video instruction has been found to be as effective as personal instruction and significantly superior to the use of IFUs in teaching correct inhalation technique.[33]

The challenge for the prescribing clinician and pharmacist

It is well known that, regardless of patient age, mastering the correct technique to use most currently available OIPs, especially pMDIs and DPIs, is poor.[34] Furthermore, if the proper method of use is taught at the time of the initial prescription, this learning must be regularly reinforced to avoid the almost inevitable deterioration of the technique learned originally by the patient (or caregiver).[35] Fortunately, there are training aids that clinicians can use to assist in the process of maintaining good inhaler operation, such as placebo inhalers produced by most manufacturers for this purpose. In addition, flow measurement devices are helpful in the assessment of the compatibility of a particular inhaler for the older patient. In particular, as an example of what can be done, the In Check DIAL (Clement Clark International Ltd, Harlow, UK) determines the velocity of the inhaled air flow when the patient inhales through its mouthpiece, and its resistance to flow can be pre-set to simulate inhalation through different types of inhalers. This latter feature is particularly useful, given the wide variety of flow resistance in the range of commercially-available DPIs. The availability of websites operated by medically-competent organizations can also augment these resources, especially for caregivers, who can review the information on a regular basis to check if they are administering the medication correctly. However, even with such in-physician office aids, it may be

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Table 2

General Considerations for Use by the Older Patient/Caregiver by OIP Type

Question	pMDI	DPI	SMI	NEBULIZER
Has the patient adequate cognitive ability to coordinate actuation with inhalation?	If not, consider a VHC, even for patients having excellent technique, because performance can deteriorate over time.	A strong inhalation is needed. Consider a pMDI, SMI or nebulizer if the patient cannot provide adequate force to overcome device resistance during inhalation.	If not, consider caregiver training and support. Otherwise, the patient may be better treated either by pMDI-VHC-facemask or nebulizer.	This is the 'fallback' mode of therapy if other inhalers are unsuitable.
Has the patient the mechanical strength to actuate the inhaler?	If not, consider an aid to provide additional mechanical advantage, especially if the patient has arthritis.	If not, consider a multi-dose DPI with integral dosing, where the need to manipulate single doses is avoided altogether.	If not, consider caregiver support and training if the patient cannot use either of these inhaler classes.	The mechanical strength limitation does not apply to actuation of nebulizers.
Can the patient use a mouthpiece to inhale?	If not, a pMDI-VHC-facemask is the best solution for patients with limited cognitive ability or with inadequate motor control, as with Parkinsonism.	If not, consider the patient for therapy by pMDI-VHC or nebulizer. DPIs, in general, are not supplied with a facemask.	If not, consider a pMDI + VHC or nebulizer. Currently, the Respimat® device does not have a facemask.	If not, consider the use of a facemask.
How should a caregiver assist patients?	Provide training for the caregiver in correct preparation of the inhaler and VHC, fitting of the facemask and actuation of the pMDI.	In the event that the patient has arthritis in the hands, but can otherwise coordinate the actuation/inhalation process, provide training for the caregiver in correct preparation of the inhaler, focusing on timing of the actuation of the inhaler with inhalation.		Provide training for the caregiver in correct preparation of the nebulizer, fitting of the facemask, and cleaning/maintenance of the device and associated equipment.
Is there a concern about ocular exposure?	If the patient has glaucoma, consider ensuring that anticholinergics are taken via SMI or VHC with mouthpiece/tight-fitting facemask.		Instruct the patient to inhale as soon as SMI is actuated to avoid aerosol cloud exposure to eyes.	If the formulation is only available for nebulization, use mouthpiece where possible, select a BAN and/or a facemask that avoids eye exposure to exhaled medication.

helpful if the prescribing clinician considers the general aspects listed in Table 2 that pertain particularly to the older patient.

Conclusions

The inhalation route of drug administration remains an important means of providing the older patient with necessary topical therapies for asthma, COPD and combinations of both diseases. Furthermore, its use to deliver drugs to the systemic blood circulation for the treatment of disease in distant organs, for example, the pancreas in type-II diabetes, is on the increase. In recent years, there have been significant improvements in the choice of formulations, and as a result, the choice of types of inhalers has widened. Thus far, much of the thrust in the development of OIPs has been focused largely on meeting the important and challenging needs of infants and small children, who have a high incidence of asthma and related allergic airway disease. Less has been done in the way of tailoring the inhaler designs to improve the quality of medication delivery for the increasing population at the opposite end of the age range.

This short article has sought to identify two separate challenges. Firstly, inhaler developers are encouraged to build-in user-friendly and enabling features at minimum added cost, which simplify the process of preparing, operating and maintaining the inhaler correctly. Such features should be supported with high quality IFUs that enable rapid and accurate assimilation of key information pertinent to their successful use. It is highly likely that improvements in design will translate into a better inhaler use experience for the general population as well as the older users. The second challenge is directed at the prescribing physician to ensure that the inhaler is selected to match the physical and mental capabilities of the patient. The clinician, likely with the support of the pharmacist, should ideally review the choice(s) made on a regular basis, especially if other aspects of the patient's physical and mental condition deteriorate markedly with time. Under such circumstances, a caregiver may need to become involved with the medication delivery process, and it follows that adequate training of such persons is also a highly desirable goal.

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