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ADD-ON INHALATION DEVICES CORRELATION AND INFLUENCE ON ASTHMATIC PATIENTS

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Asthma is a prevalent condition, and a significant number of individuals with asthma are often misdiagnosed with other diseases. Inhalation therapy, with a pressurized metered-dose inhaler (pMDI), is the most often used treatment for asthma. Spacers and valved holding chambers (VHCs) are supplementary devices for (pMDIs), specifically created to address the typical difficulties patients encounter while using a pMDI to give aerosol medication. Spacers were designed specifically to address problems that patients have with the pMDI method, such as difficulties coordinating the actuation and inhalation, as well as the occurrence of local side effects due to deposition in the oropharynx. Existing clinical guidelines recommend the broad prescription and utilization of spacers. However, patients frequently fail to utilise these devices as intended despite their ubiquitous availability. To fully comprehend the potential of spacers and VHCs in enhancing the delivery of pressurized aerosols to patients, it is essential to know their background, as well as the important factors that influence the optimization of these devices. This understanding is crucial for both current and future advancements in this field.

We also emphasize practical suggestions for the proper utilization and upkeep of spacers/VHCs, which we believe provide practical assistance and guidance to both patients and healthcare providers.

Keywords: *Asthma, pMDI, spacer, valved holding chamber, pMDI accessory device, electrostatic, inadequate inhalation technique, adherence*

INTRODUCTION

Asthma is a persistent respiratory ailment marked by inflammation and obstruction of the air passages, leading to breathing difficulties, wheezing, and coughing. "Asthma" is a more precise term than chronic inflammation of the lower respiratory tract. it includes a wide array of clinical disorders that vary in terms of their seriousness, beginning, factors that increase the likelihood, stimuli, reaction to therapy, genetics, and natural development.[1]

Asthma is a prevalent and persistent respiratory condition that impacts between 1% and 29% of individuals in various nations.[2, 3]

The incidence of asthma is increasing, impacting over 339 million individuals globally, with a prevalence rate of 12.6%. .[4, 5]

According to the National Health Interview Survey (NHIS)-2012, over 40 million individuals in the United States of America (USA) experienced asthma at some point in their lives, which accounts for 13% of the country's population. Additionally, 26 million people, or 8% of the population, now suffer from asthma.[6]

In 2019, the number of deaths caused by asthma was more than 461,000. These deaths were primarily concentrated in low and middle-income countries (LMIC), where it is difficult to diagnose asthma early and provide

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appropriate treatment. The prevalence in Egypt is approximately 6.7% of the overall population.[7]

However, this Figure may be too low, given the phenomenon of asthma being diagnosed less frequently than it occurs is widely recognized. [8]

Asthma symptoms are accompanied by intermittent obstruction of airflow during exhalation.[8]

One of the most common types of Asthma:

1- Allergic asthma refers to a condition where the airways become inflamed and narrowed due to an allergic reaction.
2- Non-allergic asthma refers to a type of asthma that is not caused by allergies.
3- There are two types of asthma-related to coughing: cough variant asthma and cough predominant asthma.
4- Adult-onset asthma, also known as late-onset asthma, refers to the development of asthma symptoms in adulthood.
5- Ongoing restrictions in the flow of air characterise asthma
6- Asthma accompanied by obesity.

Making The Initial Diagnosis

To diagnose asthma before starting treatment, it is necessary to observe common respiratory symptoms such as wheezing, shortness of breath (dyspnea), chest tightness, cough, and variable expiratory airflow limitation. This diagnosis is established by the identification of both of these symptoms.9

The presence of the following signs is characteristic of asthma and, if observed, enhances the likelihood that the patient is suffering from asthma.

- Patients, particularly adults, may suffer multiple types of symptoms.
- Symptoms frequently exacerbate throughout nighttime or early morning hours.
- Symptoms exhibit temporal and quantitative variations.
- Symptoms are elicited by viral illnesses (such as colds), physical exertion, exposure to allergens, fluctuations in weather, laughter, or irritants such as car exhaust fumes, smoke, or potent odours.

The following characteristics diminish the likelihood that respiratory symptoms are attributable to asthma:

- Presence of a cough without any accompanying respiratory symptoms.
- Persistent production of sputum over a long period.
- Difficulty breathing accompanied by feelings of dizziness, lightheadedness, or tingling in the extremities (paraesthesia).
- Pain in the chest.
- Breathlessness during physical activity with noisy breathing in.

For the initial detection of asthma in adults, adolescents, and children aged 6-11 years, a pattern of variable respiratory symptoms is often evident. Typically, these symptoms—such as wheezing, breathlessness, chest tightness, and coughing—appear inconsistently over time and vary in severity. Asthma symptoms frequently worsen at night or upon waking, aligning with natural circadian rhythms that influence airway function. Additionally, specific triggers play a significant role in provoking symptoms. Physical activities, including exercise and even laughter, can precipitate asthma symptoms, as can exposure to environmental factors such as cold air, allergens (like dust or pollen), and irritants like smoke. In many cases, symptoms intensify or become more frequent during viral respiratory infections, particularly in children, highlighting the variability that characterizes asthma and helps distinguish it from other respiratory conditions.[8]

Verified Variable Expiratory Airflow Limitation [8]

Positive bronchodilator (BD) Responsiveness (reversibility) test with spirometry (or PEF).

For adults, a significant increase in Forced expiratory volume in the first second (FEV1) or Forced vital capacity (FVC) from the initial measurement is considered to be ≥12% and ≥200 mL. However, a more reliable indication of improvement is when the rise is ≥15% and ≥400 mL. If spirometry is not available, an increase in PEF of ≥20% can be used as an alternative measure. however, There is a similarity in the response to bronchodilators and other measures of variance

between those who are healthy and those who have a disease. [10]

1. Children: a minimum rise in FEV1 of at least 12% predicted (or in PEF of at least 15%) compared to the initial measurement. Assess the difference in measurements 10-15 minutes after administering 200-400 mcg of salbutamol (albuterol) or a similar medication, compared to the readings taken before the medication was given.
2. High variability in peak expiratory flow (PEF) measurements taken twice daily over 2 weeks.
3. Improvement in lung function observed after 4 weeks of treatment.
4. Bronchial challenge test with a positive result
5. There is a significant amount of fluctuation in lung function between visits, with a high level of accuracy in identifying specific changes but a low level of accuracy in detecting overall changes.

Performing lung function testing to confirm the presence of intermittent obstruction of airflow during exhalation is indicative of asthma:

Asthma is more likely to be diagnosed in a patient with respiratory symptoms if there are more fluctuations in lung function or if an excess variation is observed often. The Technical Standards Committee has proposed modifying the criteria for a positive bronchodilator responsiveness test. Currently, the criterion is an increase in FEV1 or FVC of ≥12% and >200 mL from baseline. The recommended change is to consider an increase from a baseline of >10% of the patient's expected value as the new criterion [11]

During severe exacerbations or viral infections, as well as in cases of long-standing asthma, bronchodilator responsiveness (reversibility) may be impaired. Additionally, the effectiveness of inhaled corticosteroid treatment typically leads to a decrease in bronchodilator responsiveness. If there is no bronchodilator responsiveness detected during the initial presentation, the subsequent course of action will be determined by the availability of tests and the urgency of the need for treatment based on clinical assessment.

Global Initiative for Asthma (GINA) acknowledges that there is a lack of widespread availability of spirometry for health practitioners worldwide. [12]

It was found that individuals who did not receive pulmonary function testing at the time of initial diagnosis had a lower likelihood of having their asthma diagnosis confirmed. Two per cent of the patients had significant cardiorespiratory diseases that had been incorrectly classified as asthma before the diagnosis.[13]

A Canadian study found that individuals with undiagnosed asthma had a diminished health-related quality of life and a greater frequency of unscheduled healthcare visits compared to those without asthma, but similar to those with a confirmed asthma diagnosis.[14]

Clinical management of asthma in adults, adolescents, and children aged 6 to 11

- ASSESS the patient's management of symptoms and their susceptibility to exacerbations, deterioration in lung function, and adverse effects of medication, with a specific focus on inhaler technique and adherence. Assess the presence of other medical conditions occurring simultaneously with asthma and consider the patient's objectives and preferences. Additionally, verify the diagnosis of asthma if it has not been established yet.
- ADJUST The patient's treatment plan is determined based on these assessments. This involves the administration of non-pharmacological interventions, such as education and skills training, to manage modifiable risk factors and comorbidities. Medication adjustments are made as needed. The recommended treatment for adults and adolescents, regardless of the severity of their condition, is a combination of inhaled corticosteroids (ICS) and formoterol, which serves as both a controller and reliever medication, as shown in GINA Track 1**(Fig. 1)**

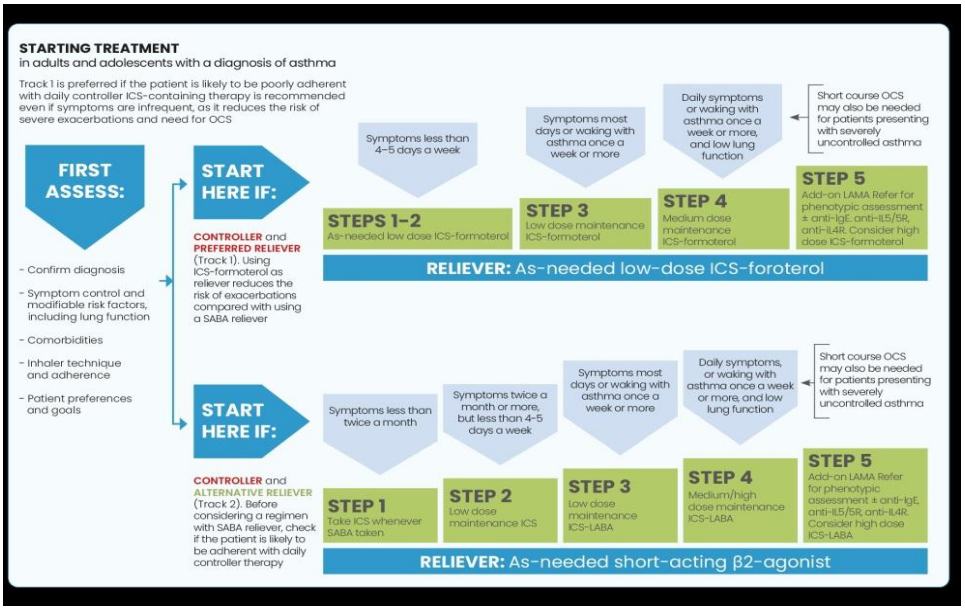

Fig. 1: Flowchart for Selecting initial controller treatment in adults and adolescents with a diagnosis of asthma.[8]
ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta2-agonist.

- REVIEW The patient should be evaluated by the treatment objectives, reassessing factors that influence symptoms, the risk of unfavourable outcomes, and patient satisfaction. Additional investigations should be arranged if necessary, and treatment should be modified accordingly.

Inhaled therapy for airway diseases

When it comes to the treatment of patients who have obstructive pulmonary disease, inhalation therapy is the foundational component. This therapy is used for both the maintenance management of chronically stable cases and as escalation or rescue drugs during acute exacerbations. [15]

Drugs that are taken orally, intravenously, or intramuscularly enter the bloodstream and can reach the majority of organs and tissues, including the airways, when they are administered according to these methods. A medicine can be delivered directly into the airways, which are the site of action in obstructive disorders such as asthma and chronic obstructive pulmonary disease (COPD). This is possible even if the medication is breathed.

This makes it possible to achieve a somewhat quicker beginning of action, while also utilizing a lower amount of the active principle and creating fewer side effects in areas where its action is not required.[16]

In addition, it is important for inhalation therapy to effectively target the entire bronchial tree, with a specific focus on the small airways known as bronchioles. These bronchioles are crucial in the development of broncho-obstructive illnesses. To accomplish this objective, the particles of the medicine must be of suitable dimensions. Particles having a diameter of more than 10 µm that are inhaled are stopped at the level of the mouth and throat. These particles can be absorbed, particularly if they are swallowed. [17]

Aerosolised Corticosteroids, β-adrenergic agonists, and muscarinic antagonists are the three types of inhaled medications that are utilized the most frequently. [18] Pressurised Metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the most common inhaler devices used
To administer aerosolised medications.

pressurized Metered-Dose Inhalers

The pMDIs were the initial extensively utilized multi-dose portable devices for inhalation therapy.[19] The delivery system can administer individual or mixed medications, such as glucocorticoids, beta-agonists, and antimuscarinic bronchodilators.

A typical pMDI consists of (**Fig. 2**):-

1. A metallic container that holds medication in a liquid or suspended form, along with a pressurized liquefied gas propellant.
2. a metering valve that enables the precise dispensing of drug doses.
3. a plastic mouthpiece enabling the patient to activate the device and deliver the particles into the respiratory system.[20]

To activate the device, the user exerts a downward force on the upper portion of the canister. The internal pressure produces enough energy to disperse and transform the drug into an aerosol, while the propellant rapidly vaporizes.

The initial pMDI emitted a plume characterized by a brief length of approximately 200 milliseconds and a rapid velocity of around 30 meters per second at the nozzle. The outcome was a significant impact in the oropharynx and a relatively low deposition in the lungs, amounting to approximately 10% of the administered dose.[21]

the most recent pMDI, which is equipped with Modulite® technology and comprises an extra-fine particle formulation has Pulmonary deposition greater than fifty per cent of the nominal dose.[22]

A further issue that arose with early pMDI was the so-called "cold-Freon effect," which refers to the initial reaction that occurs when the cold blast of MDI propellant is applied to the back of the throat. The propellant could experience a temperature drop below -20 degrees Celsius, which occasionally led to the cessation of the inhalation process.[23]

The development of pMDI was facilitated by the Montreal Protocol, which prohibited the use of chlorofluorocarbon (CFC) as a propellant due to its recognized role in the depletion of the ozone layer. The transition from chlorofluorocarbons (CFC) to hydrofluoroalkane (HFA) resulted in enhanced synchronization between hand movements and breaths, as well as improved delivery of the medication to the lungs. This improvement was achieved by reducing the speed at which the medication plume is released from the inhaler.[24]

In addition to the pMDI products that are prescribed more frequently, the utilization of pMDIs for the delivery of novel drugs is still a subject which is being researched When dealing with the management of expensive formulations, that have a narrow therapeutic range, or cause undesired local side effects, the use of a spacer may be required.

In the past, certain pMDIs like triamcinolone acetonide and flunisolide were available on the market. However, their flavours were so unpleasant that they were not authorized for sale unless used with a spacer.[25]

The utilization of spacers and reservoirs resulted in an improvement in the distribution of the drug in the lungs. [26]

Spacer devices for inhaled therapy

In the 1950s, the concept of processing the pMDI into a spacer was introduced. A spacer is an extra container positioned between the pMDI's mouthpiece and the patient's mouth. Alternatively, a valved holding chamber (VHC) was created. This chamber acts as a reservoir with a one-way valve that permits airflow into the patient's mouth but prevents it from escaping. This was done before inhaling the medication.[19]

The tube spacer developed in the late 1970s, known as Inhalet or Astra, was specifically designed to increase the distance between the mouthpiece and the patient's mouth. This design ensured that the aerosol reaching the patient's mouth would have the same speed as the normal inhalation process **Fig. 3**.[27]

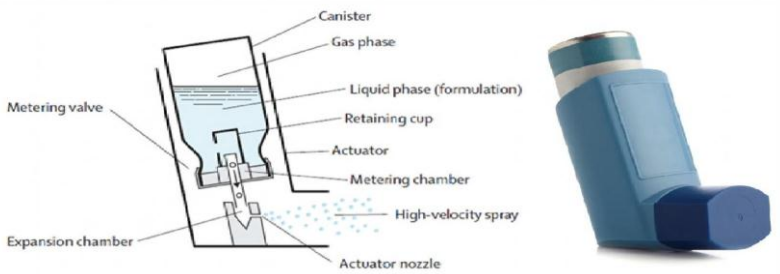

Fig. 2: Schematic design of conventional pMDIs. [72]

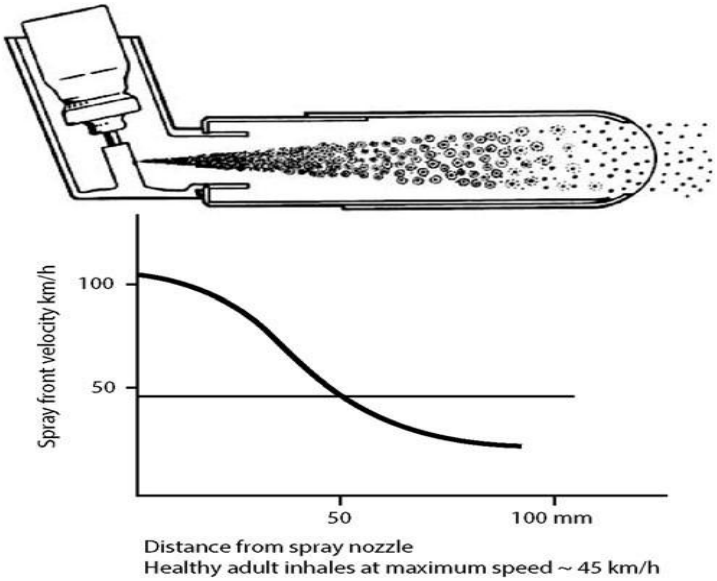

Fig. 3: Distance needed for spray to reach tidal inhalation velocity.

the use of a spacer or VHC slows down the aerosolized particles that are emitted from the pMDI to solve some of the issues and errors that could potentially be fatal when using a pMDI. This may further increase the lung deposition of the respirable fine particles. The larger particles that are emitted from a pMDI are certainly significantly filtered out, and as a result, the amount of oropharyngeal deposition that occurs is reduced. This is true even when the technique is completely perfect.[28]

All patients who utilize a pMDI for administering inhaled medications should be advised to employ a spacer/VHC for both their routine and emergency medications. This is particularly crucial for patients who struggle to synchronize the activation of the pMDI with their inhalation. This applies to children aged 3 and below who are using a pMDI with the help of a face mask.[29]

Individuals who are old, sick, or have limited understanding or physical ability In this case, the pMDI–spacer/VHC combination can be used to give these patients medications by their family members or carers.[30]

Comprehensive research has demonstrated that when there is a need to urgently administer a bronchodilator for a sudden worsening of COPD or asthma in both children and adults, using a pMDI with a spacer/VHC is just as effective and safe as nebulized therapy.[31]

Furthermore, it is possible that this intervention could effectively decrease the duration of waiting times in emergency rooms and mitigate any adverse effects associated with bronchodilator therapy. In comparison to nebulised therapy, it is also more cost-effective, convenient, portable, and requires relatively little maintenance. [26]

Although guidelines suggest that pMDIs should be utilized in conjunction with a spacer/VHC It appears that they are being greatly underused. The previous estimates varied from 10% in the UK in 1990 to 46% in Canada in 2008. [32]

In a survey conducted in the emergency department of the USA, it was found that less than 50% of patients with asthma or COPD who used a pMDI owned a spacer/VHC. Furthermore, only half of those who owned a spacer/VHC had used it on the day they presented to the emergency department.[33]

A study conducted in New Zealand found that 40% of patients with COPD used a spacer/VHC, whereas only 15% of asthma patients did.[34]

However, not all spacers are created alike; their performance might differ depending on factors such as their size or volume, shape, the material from which they are manufactured and their tendency to become electrostatically charged, how they interact with the patient, and whether or not they contain valves and feedback devices. [35]

Size-Volume

Small-volume spacers, typically with a capacity of up to 100 mL, are frequently unvalved and consist of tube-like extensions that are attached to the mouthpiece of the

pMDI. Although they are not overly cumbersome, they are also unlikely to eliminate the need for the patient to synchronize the activation of the pMDI with the onset of inhalation.
Spacers with a capacity of 100-350 mL are considered medium-sized **Table 1**, while those with a capacity of over 700 mL are considered large-volume **Fig. 4**.

These spacers generally feature a unidirectional valve located at the mouthpiece's end, enabling inhalation while blocking exhalation into the spacer. These devices are known as VHCs (Valved Holding Chambers) and offer increased flexibility in the time window for patients to begin inhaling after activating the pMDI or allowing delivery through tidal breathing. They exhibit a larger size and are less convenient to carry. Theoretical analysis suggests that a spacer/VHC should ideally have a volume between 100 and 700 mL. Furthermore, it must guarantee a minimum separation of 10 cm between the pMDI and the patient's oral cavity.[24]

The volume of the spacer/VHC can greatly affect the number of breaths needed to empty it, which is important in young infants who produce tidal breaths of 10 mL·kg−1 body weight. The size of the spacer/ VHC does not affect the fine particle fraction. [36] However, The aerosol profile can be influenced by the size/Capacity, which in turn affects the variability of the particle composition in the released dosage during inhalation. [37]

Within a spacer/VHC with a high capacity, the aerosol particles reach a state of rest before inhalation, ensuring uniform distribution of the aerosol during the breathing process. Within a spacer of limited capacity, the collection of particles continues to be in a state of turbulence, perhaps resulting in an initial release of a concentrated aerosol followed by a subsequent release of air with a lower concentration of aerosol particles. Consequently, the emission of all particles from a single pMDI activation is more likely to be decreased by minimal inhalation when using a large-volume spacer/VHC in comparison to a small-volume one. [24]

Table 1: Different spacers' characteristics.[73]

	Able	**Aer-8**	**Aerochamber plus**	**Dispozable**	**Tipshaler**
Spacer volume	210 ml	500 ml	145 ml	230ml	260 ml
Spacer dimensions	155*55*66 mm	100mm length, 50mm width	145mm length, 46mm width	107mm length, 84mm width	230*140*80mm
Electrostatic	Antistatic	antistatic	antistatic	antistatic	antistatic
N.of valves	one valve	zero	one valve	zero	two valves
Types of valves	two -way valve	-----	one-way valve	----	one-way valve
Shape	Plume shaped	Cardboard box shape	Tube shape	Cup shape	Balloon shaped tank
					

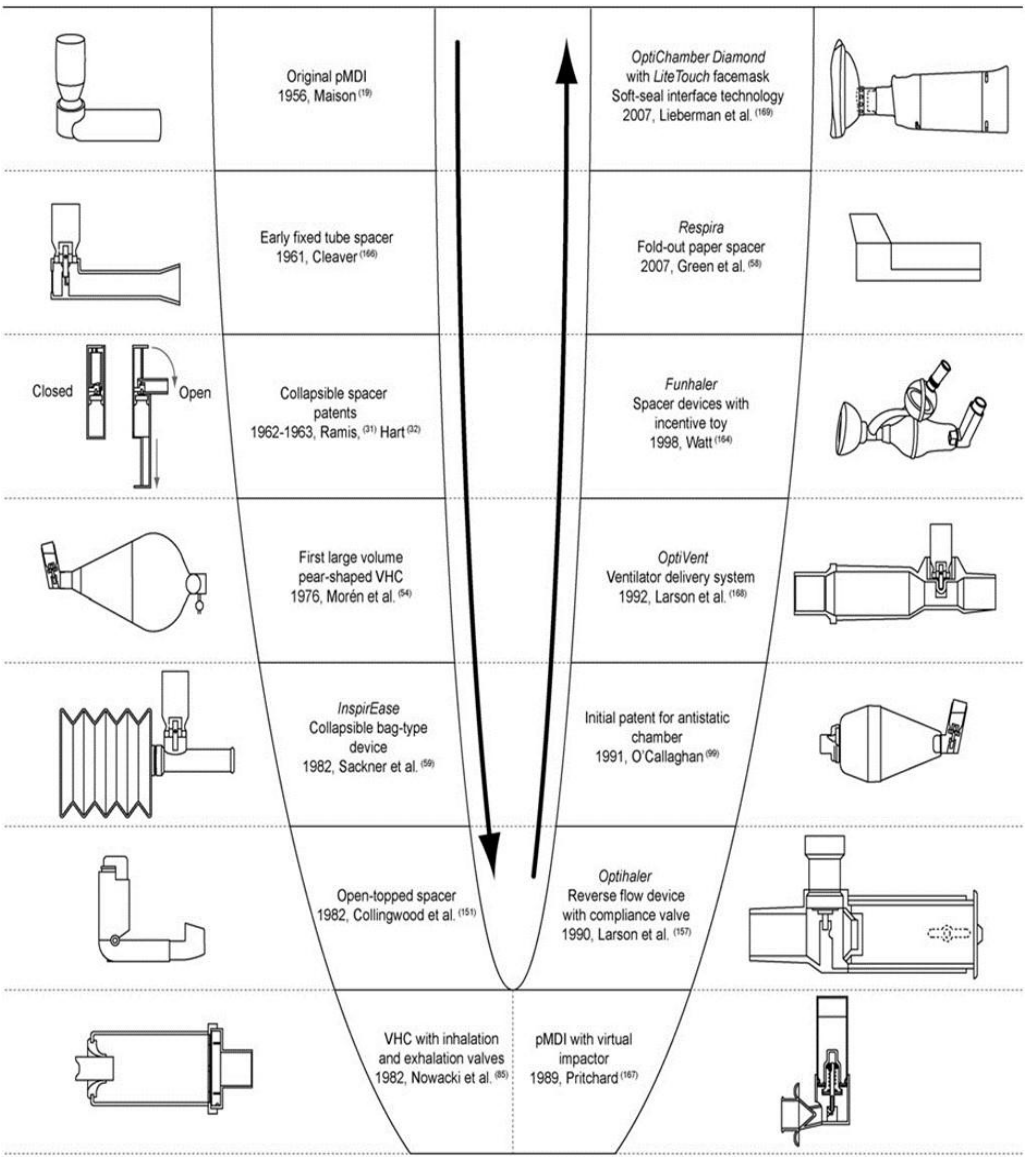

Fig. 4: Historical development of spacer design.[25]

Valves

With valve-less, open-tube spacers, the pMDI is simply separated from the oropharynx of the patient when it is inserted. VHCs are equipped with a low-resistance, one-way valve that is located behind the mouthpiece **Table 1**, **Fig. 4**. This valve is responsible for maintaining the aerosol content inside the device until the patient breathes in. Furthermore, it inhibits the re-entry of exhaled breath into the VHC. The VHC can be used with both tidal breathing and a single, deep inspiration due to this capability. A notable portion (15 out of 80 in the mentioned study) of extremely young infants (under 24 months old) cannot provide enough forceful inhalation pressure to activate the one-way valve in different commercially accessible VHCs[38]. Before prescribing, it is imperative to evaluate this capability.

Valves can get obstructed if they are dirty or damaged, which can be easily identified and potentially resolved by cleaning or replacing the device if the patient is aware of the issue.[35]

Shape

Numerous research works have illustrated that, in individuals with obstructive pulmonary disease, a sizable pear-shaped intermediary (with a dimension of 250 mm and a peak internal breadth of 130 mm) results in a more substantial enhancement in ΔFEV1 in contrast to a tube shape (with a dimension of 100 mm and a breadth of 32 mm).[39]

The emergence of high-velocity photography in the mid-1960s has enabled the subjective assessment of pMDI plumes. This optical examination has uncovered that various pMDIs release plumes with distinct morphologies. As highlighted by Barry and O'Callaghan in 1995, this discovery holds significant ramifications for the generalizability of conclusions regarding spacer configuration, particularly noting that the pear-shaped spacer layout was influenced by the hypothetical form of a pMDI mist.[40]

On the contrary, Recent commercially developed patents have encompassed a spherical device (Rondo, Leiras Takeda Pharmaceuticals, Turku, Finland)[25], a fold-down paper device (Respira, Respira Design, London, UK) [41], and inflatable bags with no fixed shape (InspirEase, Key Pharmaceuticals, Inc., Division of Schering-Plough, Kenilworth, NJ, USA).[42] Whether one particular design confers any real clinical advantage remains unclear.[25]

MATERIALS AND METHODS

Plastic, polycarbonate, and polymer spacers, also known as VHCs, lack electrical conductivity and are thus prone to accumulating electrostatic charge on their inner surface. [43]

Electrostatic charge possesses the capacity to allure aerosol particles, leading to a significant decrease (up to 50%) in the quantity of aerosol dosage that can be respired. Although it is feasible to reduce electrostatic charge and improve the deposition of aerosol in the lungs by pre-treating the spacer/VHC with multiple doses from a pMDI, this approach is inefficient in terms of drug consumption. Comparable outcomes can be attained, to a certain extent, by employing the device repeatedly and cleansing it with soapy water.[44] Once the cleaning and washing process is complete, it is necessary to allow nonconducting spacers to air dry by dripping off any excess moisture., and the inside surface should not be rubbed or wiped in any way. This will help to reduce the amount of electrostatic charge that would otherwise be re-accumulated.[35]

Steel or aluminium spacers/VHCs, along with specific plastic spacers/VHCs that have an antistatic inner lining made of electrostatic charge-dissipative material **Fig. 4**, do not need to be primed. The reason for this is that they lack conductivity and do not amass electrostatic charge. As a result, there is a rise in the weight of small particles and the settling of medication in the lungs in the form of aerosols.[38] and may theoretically enable dosage reduction, but this is not guaranteed while possibly increasing systemic exposure [45]

Patient–Spacers/VHCs Interfacing

In the 1970s, facemasks were first employed as a means of connecting spacers with young children,[46] They are now acknowledged as crucial components of spacer systems in patients who are incapable of performing the necessary respiratory manoeuvres. However, the degree to which a facemask obstructs spacer-mediated aerosol transport has only recently been recognized and is still being actively studied.

It is vital to pay close attention to various age-specific concerns in infants and young children. Infants predominantly respire through their nasal passages, leading to a 50% reduction in the volume of air that reaches their lungs.[47] Young children cannot comprehend or sustain a "breath-hold," yet it seems that regular breathing may lead to similar clinical reactions.[48] Additionally, children tend to hyperventilate while wearing a facemask.[49]

The importance of a proper facemask-to-face seal, although not specifically examined, was once again brought up in 1992.[50] A comparative study conducted outside of a living organism, known as ex-vivo, examined various facemasks and found that the design characteristics that affected the seal between the facemask and the face could play a crucial role in ensuring adequate drug administration. These design aspects also largely explain the significant variation in the amount of drug supplied.[51] In 2005, it was established that the seal between the facemask and the face plays an important role in controlling how aerosols are delivered into simulated paediatric breathing patterns. [52]

It is worth mentioning that despite the changes in sizes, dimensions, and existence of valves or faces made of non-electrostatic or

electrostatic material there is no substantial difference in patient pulmonary performance principally ΔFEV1[53]. Conversely, the material of the spacer has a notable impact on the administration of the dosage. Pharmacokinetic analysis showed that anti-static accessory devices yielded a greater quantity of aerosol compared to non-antistatic accessory devices. (urinary salbutamol).[53-55]

In the Egyptian market, the Granzia Aero Spacer, Dolphin Chamber, and Ross Max Valved Holding Chamber are three widely recognized options for enhancing the effectiveness of metered-dose inhalers (MDIs).

Granzia Aero Spacer with Aerochamber Silicone mask, Aerochamber High-quality material, Anti-drug adhesion: Ensures full dosage reaches the lungs, Available for children and adults in different sizes, Used for respiratory and asthma patients, it helps to inhale the medication with optimal efficiency and ensures the full dose of the medication is delivered.[56]

Dolphin Chamber Atomizer with non-antistatic material, volume 133ml, atomizer chamber with mask, and different sizes: small = from 0 to 18 months, medium = from 1 year to 5 years, large = 5 years[54]

Ross Max Valved Holding Chamber (AS175 Aero Spacer - Valved Holding Chamber), a Highly efficient one-way valve for easy inhalation and exhalation with a universal Backpiece, can be used with all commonly prescribed Metered Dose Inhalers, Anti-static spacer improves the delivery of MDI by inhibiting the adherence of drug to spacer wall, Soft and flexible silicone mask provides comfortable touch and reliable seal, Portable design & easy holding, Easy disassembled and reassembled for cleaning, Mouthpiece cap can protect the mouthpiece from dirt and debris when the device is not in use, This product contains no latex and BPA free, Small, medium & large facemask to cater to the different needs, Small facemask: 0-18 months, Medium facemask: 12 months – 5 yrs, Large facemask or mouthpiece: 5 yrs. + Chamber volume: 175ml.[57]

Optimal inhalation technique

A spacer/VHC is used to address the common and potentially serious issue of inadequate coordination between the activation of the pMDI and the start of inhalation. [35]

Unlike the pMDI approach, there has been less focus on improving inhalation with a pMDI with a spacer. In a study conducted in 1982, it was found that a slow inhalation at a rate of 30 litres per minute, followed by a breath-hold of 10 seconds, resulted in a higher amount of deposition in the lungs compared to either a short breath-hold after a slow inhalation or a 10-second breath-hold after a quick inhalation.[58] Similarly, a study conducted on live subjects to evaluate the delivery of medication with an extra fine pMDI found that taking a slow inhalation till reaching maximum lung capacity, and then holding the breath for at least 5 seconds, resulted in better deposition of the medication in the lungs compared to normal breathing.[59]

Thus, it is advisable for individuals with the ability to do so to inhale gradually and retain their breath. However, studies have shown that children aged 5 to 7 experience a significant improvement in lung function when they perform five tidal breaths using a large-volume pear-shaped spacer called Nebuhaler in **Table 2**. [60] Two tidal inhalations using a spacer are usually enough to empty a standard small-volume spacer in youngsters between the ages of 2 and 7.[36] Manufacturer instructions typically advise doing two slow and controlled inhalations, which can be challenging. [25]

Table 2: Optimal inhaler technique of pMDI and spacers.[60]

Put the metal canister into the "boot" making certain it is seated correctly. *
Remove the cap off from the mouthpiece. *
Shake the inhaler up and down 4 to 5 times. *
Check that the device does not contain any foreign matter. *
If you are starting a new inhaler or have not used the inhaler for more than one week, point the mouthpiece away from you and press the canister to release one dose into the air.
Hold the inhaler in its upright position (with the mouthpiece at the bottom).
Assemble the Spacer *
Insert the mouthpiece of the inhaler into the flat end of the Spacer. *
Breathe out to the end of a normal breath for non-VHCs
Hold the spacer by the MDI vertically
Put the mouthpiece in your mouth, past your teeth and above your tongue. Close your lips around the mouthpiece so that the medication does not go into your eyes.
Sit upright and Keep your chin up.
While breathing in slowly and deeply through your mouth, fully press down once on the top of the metal canister of your inhaler. * for non-VHCs
Breathe normally and slowly, in and out, many times. * for VHCs
Hold your breath for 5 to 10 seconds for non-VHCs
Breathe out slowly
Remove the Spacer ®from your mouth.
If you take more than one spray, wait 15 to 30 seconds (or as directed in the package insert) before taking the next puff. Then repeat steps 3-9
Remove the inhaler from the spacer
Replace the cap on the mouthpiece after you are finished.

*** critical steps[63]**

Prevalence of Incorrect Inhaler Technique

Improper use of inhalers has lasted for the last four decades. The "correct" method refers to the performance of all processes accurately. The "acceptable" technique means that around 80% of the steps were done correctly and no major mistakes were noticed. The "poor" approach indicates the presence of one or more critical errors and/or errors in more than 50% of the inhalation procedure phases **Fig. 5**

Incorrect utilization of various inhalation devices might potentially result in compromised management of asthma, leading to poorer control of the condition **Fig. 6-7** [61]

Customizing the selection of a device is essential for achieving the best treatment outcomes. The chosen device should be tailored to the patient's specific disease characteristics and be one that they are likely to use consistently. This will encourage adherence to their asthma medication and help them achieve their asthma management goals. [8]

There is a strong correlation between reduced errors in handling inhalers and increased patient preference for a certain device. [62]

An empirical study conducted on actual patients with asthma revealed that a greater degree of patient contentment with their inhaler device was linked to enhanced adherence and superior patient-reported outcomes. These outcomes encompassed an improved standard of living, and a decreased frequency of exacerbations **Fig.** 7.

Prior research has established a correlation between mistakes in using inhalers and more severe disease outcomes, which aligns with earlier findings regarding MDIs in asthma and COPD. [61]

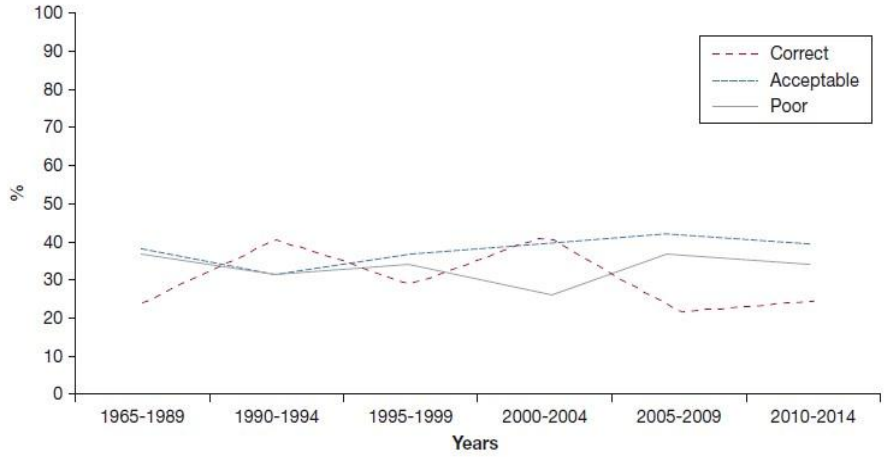

Fig. 5: shows the average of correct, acceptable, and poor tests over the 40 years of observation.

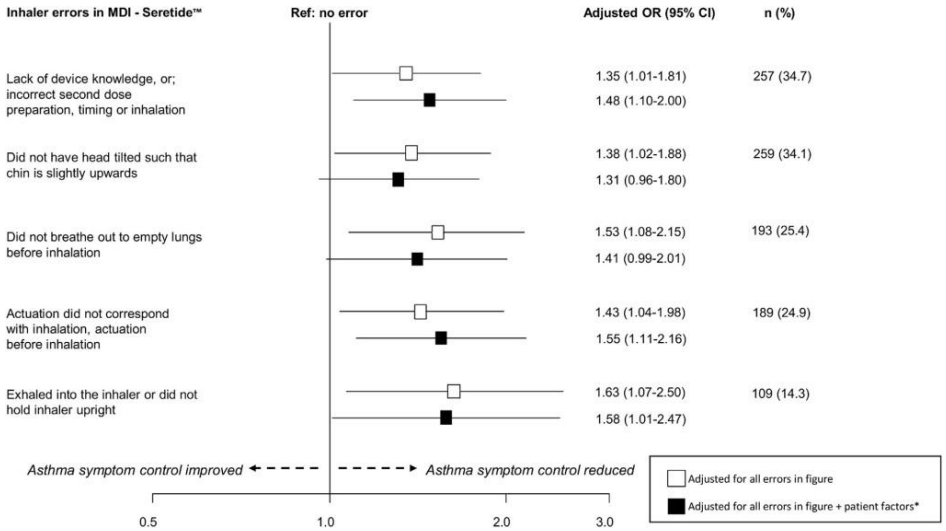

Fig. 6: Association between inhaler errors (for MDI) and uncontrolled asthma. BMI, Body mass index; Ref, reference group in logistic regression. *Patient factors used to adjust were age, sex, smoking status, BMI, rhinitis, and paracetamol use.[63]

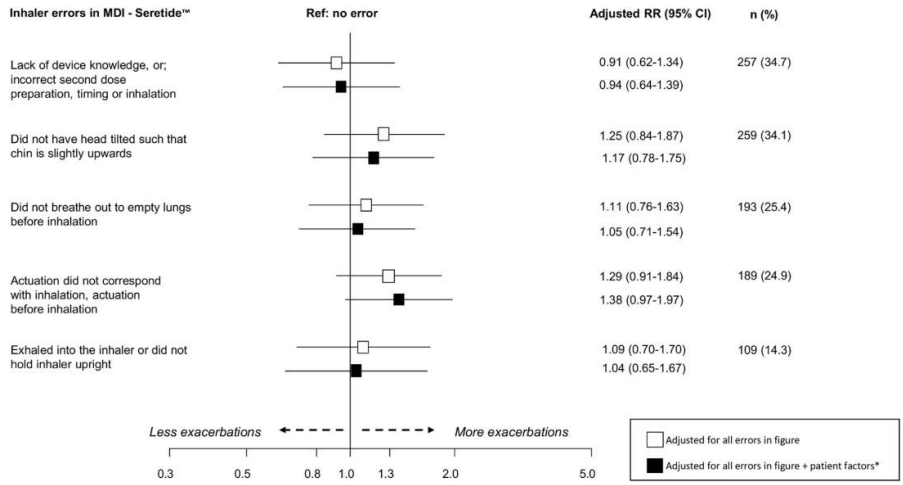

Fig. 7: Association between inhaler errors (for MDI) and rate of exacerbations. BMI, Body mass index; Ref, reference group in Poisson regression. *Patient factors used to adjust were age, sex, smoking status, BMI, rhinitis, and paracetamol use.[63]

In the CRITIKAL study, the errors related to the inhaler, such as inadequate inhalation effort, failure to exhale completely before inhaling, not holding the breath, and erroneous administration of the second dose, were found to have strong correlations with uncontrolled asthma in univariable analysis. After conducting a multivariate analysis and accounting for adherence, it was found that insufficient inspiratory effort was still a significant factor independently related to uncontrolled asthma.[63]

Only two specific studies have provided information on the correlation between the incorrect use of inhalers and the worsening of symptoms. [63, 64]

MDIs were significantly impacted by errors specifically associated with the administration of the second dose. This entailed forcefully expelling air into the inhaler before preparing the subsequent dose, inhaling a second time from the initial dose without preparing the subsequent dose, and neglecting to wait for a minimum of 30 seconds between inhaling the first and second doses (to allow the chamber to replenish). **Fig. 6** [61]

Failure to exhale before inhaling and failure to hold the breath are common mistakes that apply to all devices. Research indicates that performing an exhalation before inhalation and holding one's breath can result in increased lung deposition **Fig. 6-7**.[65]

An additional inhalation technique involves not tilting the head slightly back, which is recommended to guarantee that the drug particles are effectively carried along with the inhaled airstream. This mistake was linked to unmanaged asthma. **Fig. 6-7** [61]

It is recommended to inhale slowly when using MDI devices to get better delivery of medication to the lungs. This technique has been associated with an increase in the quality of life for patients who have strong coordination. **Fig. 6-7** [59]

The study revealed an important error in the use of MDI, specifically the absence of synchronization between the start of inhalation and the administration of the dose (with the dose being released before inhalation). The CRITIKAL study findings highlighted that a significant error related to the use of MDI is exhaling into the mouthpiece or not keeping the inhaler in an upright position. **Fig. 6**.[66]

Adherence and Compliance

The suboptimal therapeutic response can be attributed to patient-related issues, specifically non-adherence and non-compliance. Adherence, in this context, pertains to a patient's desire to comply with a prescribed regimen or utilize a device as instructed. Compliance, also known as competence, pertains to the accurate utilization of a treatment or device.

‘‘True adherence’’ [(% adherence to prescribed regimen · % compliance with correct device use)/100] is a measure of a patient’s overall device use. Assessing true adherence allows us to differentiate between inadequate adherence and inadequate compliance. [67]

Evidence shows that patients who have been educated on the proper utilization of inhalation devices, either through in-person training or video tutorials, exhibit superior adherence compared to those who only received written instructions. [68]

Due to the challenges associated with using accessory devices correctly and consistently, there have been several efforts to integrate compliance aids related to spacers into their design and production.[25]

These additional devices are designed to facilitate storage and make aerosol visible to the patient in case of an uncoordinated inhalation. A spacer equipped with a visual incentive device, aimed at enhancing both adherence and compliance, has been recently developed. [69]

Pharmacoeconomic aspect

Bronchodilators and steroids administered via pMDI have shown therapeutic equivalence in terms of dosage cost, typically being one to two times cheaper than other aerosol administration devices. [70]

it was determined that converting from small-volume nebulisers to holding chambers in their 600-bed tertiary referral hospital would result in an expected yearly savings of approximately US$400,000. By applying the same analysis to comparable institutions across the United States, they determined that the potential yearly cost reduction for this treatment approach might reach approximately $200 million.[25]

a previous study showed a cost advantage when utilizing pMDIs as opposed to small-volume nebulizers in the emergency room.[26]

Despite the abundance of evidence supporting the use of pMDI plus spacers to produce bronchodilator aerosols for treating acute asthma attacks in the emergency department, it is astonishing that the nebulized method remains the primary approach for administering bronchodilators to asthma patients in this setting. This is particularly surprising considering the time and cost savings associated with the pMDI plus spacer approach.[71]

METHODS

For this review, data was collected from various online medical databases. The primary database utilized was PubMed, Cochrane Library, Ovid and Google Scholar. The search was conducted using Medical Subject Headings (MeSH) terms, including "spacers," "valved holding chambers," "metered-dose inhalers," "asthma therapy," and "inhalation devices."
The inclusion criteria for the studies were as follows:
- Publications available in the English language.
- Studies published between 2000 and 2023.
- Articles focusing on the use of spacers and valved holding chambers in asthma and respiratory therapies.

Conclusion

The development of spacers has had an intricate progression, shaped by scientific, commercial, and therapeutic perspectives. Currently, the guidelines suggest that all children utilizing a pMDI, as well as any patient receiving inhaled corticosteroids, and those with the uncertain capacity to coordinate or complete a breathing technique, should be provided a spacer or VHC. Modern systems can reduce the impact of problems including delay in inhalation, static charge, and reliance on tidal breathing. Nevertheless, even after over 50 years of progress, the refinement of spacer design is still unfinished. There is a clear indication that auxiliary devices are not popular among patients. Ideally, the spacer should have a smaller size, making it easily portable and less noticeable when being used, to enhance the user-friendliness of spacers.

Future Research Directions

Based on the findings of this review, several areas warrant further investigation to enhance the understanding and optimization of spacers and valved holding chambers in respiratory therapy. Future research should focus on the following directions:

- Device Design and Material Improvements: Investigate new materials and designs for spacers and VHCs to enhance drug delivery efficiency, reduce electrostatic charge, and improve patient comfort and compliance.
- Comparative Studies Across Age Groups: Conduct comprehensive studies to assess the effectiveness and ease of use of different devices across various age groups, especially in young children and elderly populations.
- Long-Term Patient Outcomes: Explore the long-term outcomes of patients using different types of spacers and VHCs to better understand the impact of these devices on quality of life and asthma control over time.
- Technological Integration: Examine the potential for integrating digital feedback systems within spacers and VHCs to provide real-time inhalation guidance and improve correct usage.
- Patient Education and Adherence: Research into effective educational interventions is needed to improve patient adherence, particularly focusing on simplifying device usage and providing clear instructions.

These research directions are critical for advancing respiratory therapy and optimizing patient outcomes, addressing the gaps identified in this review, and encouraging innovation in spacer and VHC technology.

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العلاقة والتأثير لأجهزة الاستنشاق الإضافية على مرضى الربو

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الربو حالة شائعة، وكثيرًا ما يتم تشخيص عدد كبير من الأفراد المصابين بالربو خطأً بأمراض أخرى. العلاج بالاستنشاق، باستخدام جهاز استنشاق بجرعات مقننة مضغوطة(pMDI) ، هو العلاج الأكثر استخدامًا للربو. تعد الفواصل وغرف الاحتفاظ بالصمامات (VHCs) أجهزة تكميلية لـ (pMDIs)، تم إنشاؤها خصيصًا لمعالجة الصعوبات النموذجية التي يواجهها المرضى أثناء استخدام pMDIلإعطاء الدواء الهباء الجوي. تم تصميم الفواصل خصيصًا لمعالجة المشاكل التي يواجهها المرضى مع طريقة pMDI ، مثل الصعوبات في تنسيق التشغيل والاستنشاق، فضلاً عن حدوث آثار جانبية محلية بسبب الترسيب في البلعوم الأنفي. توصي المبادئ التوجيهية السريرية الحالية بالوصف والاستخدام الواسع النطاق للفواصل. ومع ذلك، على الرغم من توفرها في كل مكان، يفشل المرضى غالبًا في استخدام هذه الأجهزة على النحو المقصود. لفهم الإمكانات الكاملة للفواصل وأجهزة التحكم في الضغط في تحسين توصيل الهباء الجوي المضغوط للمرضى، من الضروري أن يكون لديك معرفة بخلفياتها، فضلاً عن العوامل المهمة التي تؤثر على تحسين هذه الأجهزة. هذا الفهم أمر بالغ الأهمية للتقدم الحالي والمستقبلي في هذا المجال.

كما نؤكد على الاقتراحات العملية للاستخدام السليم للفواصل ، والتي نعتقد أنها توفر المساعدة العملية والتوجيه لكل من المرضى ومقدمي الرعاية الصحية.