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Inhalation Therapy in Asthma and Copd: Challenges and Measures to Overcome

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Abstract
Respiratory diseases are some of the most common diseases globally due to the higher chances of infection compared to other systems, which are relatively more isolated. Since respiratory diseases hinder breathing, their symptoms are felt more acutely, and getting drugs to their targets is a considerable challenge. In addition, changes in lung physiology due to diseases hinder the delivery and action of drugs. The upper airways are easier for drugs to reach, but deeper lung tissue may be affected by mucus hypersecretion or thickening, changes in airway diameter, fibrosis, and poor blood circulation. In this review paper, we quickly cover COPD (Chronic Obstructive Pulmonary Disease) and asthma, two of the most frequent respiratory ailments worldwide, and then go into further detail about inhalation treatment, which is the recommended technique for controlling asthma and COPD. This article includes the challenges that come with this therapy, such as the lack of patient education regarding inhalation therapy and neuro-motor difficulties, such as hand-breath coordination. We also mention solutions that have been proven to help with these challenges and the economic impact of the ineffective use of inhalation devices.
Keywords -Asthma, COPD, hand-breath coordination, dry powder inhalers, pressurized metered dose inhalers

INTRODUCTION

Respiratory disease, also recognized as lung disorder or pulmonary disease, is an acute or chronic illness that affects the respiratory system and includes lung cancer, pneumonia, pulmonary fibrosis, COPD, and asthma [1].

Asthma is a chronic condition that makes breathing challenging because the bronchial airways in the lungs enlarge and narrow, as seen in Figure 1. Fast breathing, breath shortness, chest tightness, coughing, and wheezing are all symptoms. Pet hair, dust, smoking, pollen, mold, cold air, exercise, or stress could all cause an asthma attack [2].

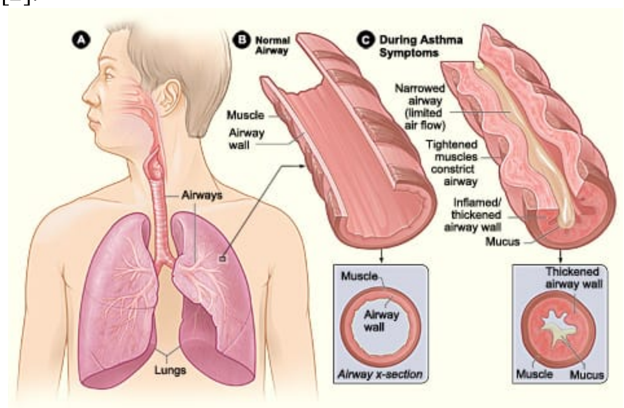

Figure 1: Effect of asthma on lungs

Children are most often affected by asthma, which is a serious NCD ("Non-Communicable Disease"). Asthma harmed a predicted 262 million people in 2019 and killed 455,000 individuals. Because of its ease of use, inhaled medicine helps manage asthma symptoms and allows patients with asthma to continue a normal, active life. Avoiding asthma triggers can help prevent asthma attacks, but it might be challenging given today's lifestyle and pollution levels. Inhalation treatment then makes symptom management easier and allows patients to live a normal, busy life. Asthma-related mortality is common in low- and lower-middle-income countries, with limited education and healthcare facilities, making diagnosis and treatment challenging [3].

COPD, often recognized as emphysema and chronic bronchitis, is a collection of disorders that cause airflow obstruction and breathing issues [4]. COPD produces airway inflammation, which destroys the tissue and lining, as seen in Figure 2.

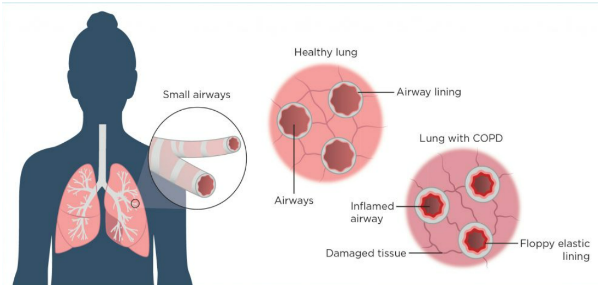

Figure 2: Difference between a healthy lung and a lung with COPD

3.23 million people died from COPD in 2019, making it the third highest cause of death worldwide. Approximately 90 percent of COPD deaths in people under the age of 70 take place in low- and middle-income nations, with tobacco smoking accounting for 30 to 40 percent of COPD cases in low as well as middle-income countries and more than 70% of cases in high-income countries [5].

Inhalation therapy

Inhaler therapy has gone a long way, from smoking herbs over 4000 years ago to the introduction of metered dosage inhalers and nebulizers, particularly in asthma treatment, COPD, and respiratory infections [6]. When inhaled, medications can be given directly into the airways using specific devices like pMDI ("Pressurized Metered Dose Inhalers") and DPI ("Dry Powder Inhalers"), which discharge the pharmaceuticals in a form that is easily absorbed by the lungs [7].

Pressurized meter dose inhaler

The most widely recommended device for administering inhaled medicine is the pressurized meter dose inhaler (pMDI). They provide a predetermined pharmaceutical dose through a pressurized canister designed to generate a fine mist of the drug (either in suspension or solution) of less than 5 microns, containing a blend of the drug and propellant [8]. It should be noted that pMDIs rely on hand-breath synchronization to deliver drugs effectively. Figure 3 depicts the mechanism of pMDI.

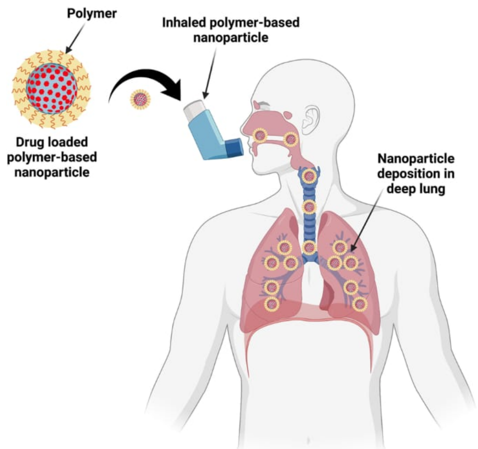

Figure 3: Mechanism of pMDI

Steps to use Pressurized Metered Dose Inhaler
The steps to use pMDI are summarized in the following Figure 4:

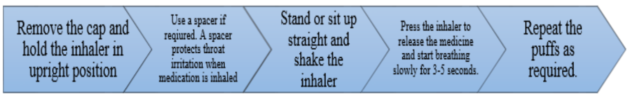

Figure 4: Steps to use pMDI

Dry powder inhalers
DPIs, as opposed to pMDIs, are breath-activated devices that deliver dry powder aerosol, either alone or in combination with a suitable carrier, to the lungs [9]. These inhalers were created to alleviate the coordination issues that pMDIs have with chlorofluorocarbons (CFCs).

DPIs are offered in either unit dosage or multi-dose configurations. A single dosage of dry powder aerosol is contained in a capsule in unit dose devices, which is placed on the device by the patient before use and is opened to release the powder for inhalation upon device activation. In multi-dose devices, it consists of several doses packaged in blister packs or multiple unit doses sized in blister strips that may travel through the inhaler [8]. Figure 5 shows the DPI method.

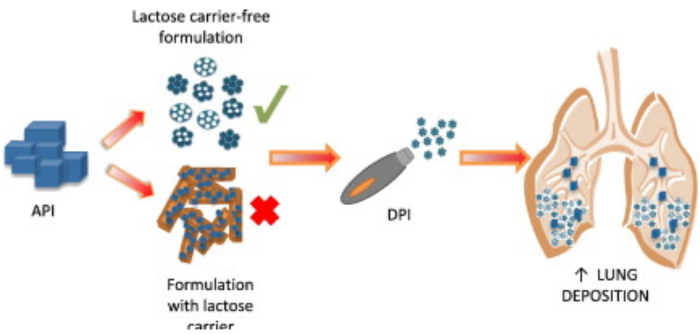

Figure 5: Mechanism of DPI

Steps to use Dry Powder Inhaler
The steps to use DPI are summarized in the following Figure 6:

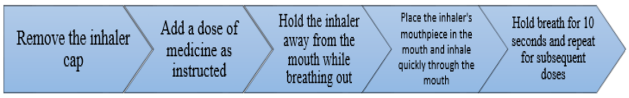

Figure 6: Steps to use DPI

Treatment
The following drugs can be used in the treatment of COPD:

- **Bronchodilators:** salbutamol, terbutaline, salmeterol, formoterol, ipropropium bromide
- **Mast cell stabilizers:** sodium cromoglycate
- **Corticosteroids:** beclomethasone, disproportionate, fluticasone, propionate, fluticasone, budesonide.

Table 1 depicts the various inhalers available for use:

Table 1: Commercial Inhalers

Brand name	Drug combination	Strength	Dose	Type of Inhaler
Advair Diskus	Fluticusone/ salmeterol	Per inhalation 100µg fluticasone/ 50µg salmeterol 250µg fluticasone/ 50µg salmeterol 500µg fluticasone/ 50µg salmeterol	1 inh Q 12 h*	Dry powder Inhaler
Symbicort HFA	Budesonide/ formoterol	Per inhalation 80µg budesonide/ 4.5µg formoterol 160 µg budesonide/ 4.5µg formoterol	2 inh Q 12h*	Metered Dose Inhaler
Intal	Sodium cromoglicate	5mg	5mg	Metered Dose Inhaler
Beclate	Beclomethasone/ disproportionate	200mcg / dose	200meter dose	Metered Dose Inhaler
Bricanyl turbolhaler	Terbutaline	500mcg	0.5 mg/dose	Dry powder Inhaler
Duolin HFA	Ipratropium bromide/ salbutamol	Per inhalation 20µg ipratropium bromide/ 100µg salbutamol	200 Metered se	Metered Dose Inhaler
Duolin	Ipratropium bromide/ levosalbutamol	Per inhalation 20mcg ipropropium bromide/ 50mcg levo salbutamol	200 meter dose	Metered Dose Inhaler

CHALLENGES

Despite its benefits, inhalation treatment has certain downsides that may jeopardize proper medication delivery and activity. Indeed, natural lung defense systems may operate as immunological, chemical, or mechanical barriers to inhaled medication particles. These will be addressed more on the next pages.

Mechanical barriers

The human respiratory tract comprises the alveolated airways, tracheobronchial airways, and extrathoracic airways, with the nasal passages serving as an effective filter for aerosol delivery into the lungs. Inhalation is ideally done through the mouth to ensure particles bypass airway bifurcations and reach the target epithelial location. Natural lung protective mechanisms act as barriers to inhaled medication particles, including mechanical, chemical, and immunological defenses.

The particle deposition within the lungs is affected by inhalation parameters like breath-hold pause, volume, and flow rate. Different inhaler types have specific recommendations for inhalation techniques. Less than 20 percent of the dosage is delivered by maximum inhalers into the lungs, with the majority being delivered into the oropharynx (for DPIs and pMDIs) or remaining in the device (for nebulizers).

In conditions with airway restrictions, such as bronchoconstriction, irritation, and excessive mucus production, mechanical barriers can further impede airflow and cause blockages, including mucus plugs. These mechanical limitations affect medication deposition.

Chemical Defenses

Chemical compounds like surfactants and proteolytic enzymes can hinder medication distribution within the lungs. Proteolytic enzymes, including neutral endopeptidase and cathepsin H, have the ability to hydrolyze proteins and peptides present within the lungs, leading to their inactivation [15].

Immunological Barriers

Undissolved drug particles have the potential to interact with alveolar macrophages, which are the primary phagocytic cells responsible for clearing inhaled debris [16]. Alveolar macrophages act as an immunological barrier without differentiating between potentially harmful or beneficial compounds [11]. Ideally, drug particles should be engulfed by macrophages and eliminated from the lungs through mechanisms such as the lymphatic system or by being transported to the lower parts of the mucociliary escalator. While the impact of macrophages on medication absorption was shown in animal models, their precise role in humans is not yet well understood [15]. Surfactants also play a role by preventing inhaled debris from adhering to lung surfaces, facilitating easier access for macrophages to clear them [11]

Behavioral impediments

Behavioral obstacles are those faced by patients themselves as a result of non-adherence to treatment regimes and poor inhaler practices, which can be attributable to misunderstanding instructions or a lack of patient education, both of which will be discussed further in the following pages.

Noncompliance with the Treatment Regime

Adherence is described as the number of doses taken in relation to the number of doses given [17]. Delivery of drugs to the lungs is strongly based on what patients do or do not do with the inhaler devices [18]. Patients frequently fail to adhere to treatment regimens, either consciously owing to the relief of their symptoms or inadvertently because they forget [19]. Cultural influences and beliefs influence how carefully a patient adheres to their treatment regimen.

Inhaler method

Because of the coordination necessary to activate the inhaler while breathing deeply and slowly, the accuracy required for the inhaler method alone may offer difficulty to a few people. Other issues addressed by DPIs include reduced inhalation force and device-specific handling faults like erroneous device alignment. Because of weakened inspiratory muscular power, the elderly are more vulnerable to a lack of inhaling force [20]. Failure to completely exhale before inhaling [21] as well as inadequate breath hold intervals after inhaling [22] are issues shared by both inhaler types.

Factors to be considered in clinical trials of inhalation therapy

Multiple elements must be considered in clinical studies of inhalation treatment, including the nature and activity of the medications in relation to the devices with which they are coupled as well as their combined safety. The patient's adaptability and convenience of usage are important considerations.

Drug-device compatibility

Participating in inhalation studies may be hindered by various barriers, including the potential for withdrawal symptoms and bronchospasm triggered by medication or non-drug factors. Additionally, individual differences in breathing patterns and the presence of comorbidities can significantly affect drug bioavailability and impact trial outcomes. For instance, the short half-life of epoprostenol, lasting only 3 to 5 minutes, requires frequent nebulization at extended intervals, posing challenges in terms of control and administration over time [23].

Concerns about safety

Poor drug solubility and bioavailability have resulted in the cancellation of several inhalation clinical studies because they allow unsafe levels of undissolved medicines to collect within the systemic circulation [24].

Patient education and flexibility

Effective treatment necessitates the patient's ability to appropriately utilize the inhaler. Because many patients perceive inhalation treatment to be complex, it needs actual demonstration and regular follow-up by clinical specialists for optimal drug delivery. It has been found that improper usage of inhalers is a cause of inadequate respiratory illness control.

Mebrahtom M et al discovered in a study at a university health center in Northwest Ethiopia that insufficient knowledge about MDIs resulted in device mishandling by around 71% of the participants, resulting in poor bronchial asthma management [25]. When compared to DPI, 18 patients had more difficulties using MDI. Arora P et al reported 95% errors in the use of MDIs by patients vs 82% errors in the use of DPI in research [26].

India's regulatory law framework

Specific regulatory recommendations for inhaled drugs have not been provided by the CDSCO ("Central Drugs Standard Control Organization") and the DCGI ("Drug Controller General of India"). In India, inhalation clinical tests must adhere to Schedule Y and Rules 122A to E of the "Drugs and Cosmetics Act" of 1945, as well as follow Good Clinical Practices (GCP) and ethical principles for conducting biological investigations involving human participants. Inhalation studies are conducted in a manner consistent with the principles applied in bioavailability and bioequivalence research [27].

LIMITATIONS IN INHALER USAGE

In the study performed by Sulaiman et al. [28], it was observed that errors related to inhaler usage primarily revolved around issues such as incorrect inspiratory flow, improper inhalation duration, lack of coordination, inadequate dose preparation, inadequate exhalation before inhalation, and insufficient breath-holding after inhalation maneuver

Problems in Pediatric Patients

Children may face challenges when using inhalers due to distractions and difficulties in learning the proper inhalation technique. As per the GINA guidelines, pressurized metered-dose inhalers (MDIs) with a volatile halogenated compound (VHC) are the recommended delivery method for pediatric asthma patients, either with or without a face mask based on the age of the child. However, the dose delivered by the VHC may vary across different models due to variations in pediatric respiratory patterns. Children, who rely solely on tidal respiration, may find it particularly challenging to grasp the duration and technique of inhalation, resulting in variability in the intake time for the complete dose intake. Younger children may prefer lower volumes of medication [29].

In cases where children are unable to use inhalers due to factors such as acute psychological stress during emergencies, comorbidities, maturity, age, or nebulizers are recommended instead [30]. Several research studies support the use of nebulizers in pediatric cases. For example, Iramain et al. found that administering ipratropium/salbutamol using MDI with VHC and a face mask was more efficient than nebulization in treating severe acute asthma exacerbations in 103 children (aged 2-14 years) admitted to the emergency room [31]. Similarly, Snider et al. carried out work on 890 individuals (aged 2 to 17 years) with mild to severe bronchial asthma exacerbations and found that MDI albuterol treatment was not inferior to breath-actuated albuterol nebulizer treatment [32].

Problems in Geriatric Patients

Coordination and cognitive deficits, which contribute significantly to inhaler usage in elderly patients, can be addressed through targeted education [33, 34]. Shirmanesh et al. confirmed rheumatoid arthritis patients' lower ability to manually complete all procedures to operate their [35]. Age-related disorders such as muscle-eye coordination, arthritic troubles, vision impairments, neurological issues (including Parkinson's disease & post-stroke status), and cognitive struggles may also offer difficulties. The new development of breath-actuated SMIs and MDIs, which may be actuated by modest airflow rates, are especially useful in older or arthritic patients who have difficulty coordinating actuation with inhalation. In fact, they are beneficial in patients of all disease severity levels.

While considering DPI treatment, it is critical to evaluate the patient's PIF ("Peak Inspiratory Flow") capability. It was demonstrated in COPD patients that the use of DPI devices causes changes in PIF and hence possible differences in drug deposition [36].

PROBLEMS WITH INHALERS

While DPIs and pMDIs are extremely easy devices to use, their proper application is not entirely obvious, and all have technological limitations that may limit efficacy. Each form of inhaler has its own set of instructions for use. The variances in device usage may confuse patients and result in a loss of medicine given owing to poor device administration, which is problematic because no one manufacturer presently produces an inhaler that can deliver the whole spectrum of medication for the diseases management like COPD and asthma in the same single inhaler, forcing the patient to learn how to operate numerous devices, each with its own unique instructions for effective use.

Problems with PMDIs

pMDIs pose considerable issues in their usage, specifically the requirement of hand-breath coordination and a low inspiratory rate (< 30 L/min) [37]. But this can still be solved by training patients over 6 years of age to coordinate actuation (which can be done in as little as 6 minutes) and using breath-actuated pMDIs to solve the issues posed by the need for hand-breath coordination.

To achieve dose invariability and consistency, pMDIs are needed to be shaken properly and actuated or 'primed' before use. Another major hindrance in the use of pMDIs is temperature. A canister temperature below 15 ºC significantly reduces emitted dose, which is an issue common to patients prone to bronchospasms in winter as they tend to keep their inhalers in the outer layers of their clothing for easy access. In fact, dose delivery by CFC pMDI in such cases would be more effective if the inhalers were kept in the inner layers of their clothing and protected from extreme external temperatures.

A graphical representation of the comparative frequency of occurrence of errors in pMDI use is shown in Figure 7:

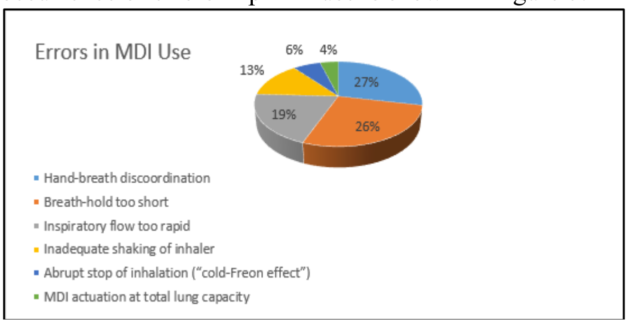

Figure 7: Errors in MDI

Challenges with DPIs

The existing DPI (Dry Powder Inhaler) devices are designed as passive systems, where the patient's inspiratory effort gives the mechanical power to release the medicine from the inhaler. However, these devices need a specific inspiratory flow rate of 30 to 90 L/min to ensure effective drug delivery. If the patient fails to generate the minimum inspiratory flow, the inhaled dosage may significantly decrease [38].

For young children, particularly those under the age of five, maintaining the necessary flow rate for effective DPI utilization can be challenging. Therefore, DPIs are generally not recommended for children in this age group [39, 40].

Exhaling directly into a DPI can also impact drug delivery. Exhaled gas could disrupt the powder in the chamber, making it unsuitable for inhalation. Additionally, the moisture in the exhaled breath could cause the carrier or medication to clump together, decreasing the ability to form individual respirable particles [38].

Proper orientation of the DPI is crucial to ensure the dosage remains in the dosing chamber and inhalation stream. Failing to prime the inhaler, open the blister pack, or pierce the capsule can result in no medication being delivered to the patient. Every device has its own specific priming procedure, and with maximal inhalers, the process is typically straightforward.

It is essential for healthcare experts to educate patients on the correct use of DPIs, including maintaining the appropriate inspiratory flow rate, avoiding exhaling into the device, and following specific priming instructions. These measures can help optimize drug delivery and ensure effective treatment outcomes.

Problems in patient education

Most patients seek healthcare when the intensity of their symptoms has reached the peak of their tolerance. As a result, they turn up to healthcare centers in sickness while frustrated, exhausted, and in fear of the news they dread to receive.

With their physical health at a low, and their mental health exhausted, it is common to see reduced levels of attention and retention of new information in patients suffering from especially taxing health issues such as chronic pulmonary diseases. The extensive diagnostic procedures and instructions regarding treatment and therapies prove to be another comprehension challenge for such patients. The patients in the worst stages of their diseases are usually those whose educational level is below the national average, and thus do not recognize, or even know of, the diseases they suffer through. Explaining their therapeutic plan is especially difficult in such cases. Patients with low literacy levels may be apprehensive in accepting the severity and suggestive cause of the disease they suffer and prognosis-especially if it is a grim prognosis. Differences in language and dialect are other barriers to overcome. Often, even a citizen with average literacy would find it difficult to follow their care provider’s language and may be embarrassed to admit it. Patients may seek treatment in places with different state languages, making it difficult for them to understand written instructions; such as those for taking pills with meals and maintaining and using aerosol devices.

A relative summary of the problems in patient education and those in clinician testing is outlined in Table 2.

Table 2: Patient education and clinician testing- Challenges on both ends

Patient Education Problems	Clinician Testing Problems
Low literacy	lack of experience with a certain equipment
Poor attention span, particularly when sick	Poor training techniques
Insufficient time to learn	Insufficient time to teach
Patient hesitant to ask questions	Poor training materials
Inadequate follow-up	Lack of follow-up

THE ECONOMIC COST OF INHALER MISUSE

Each year, over 500 million medical inhalers are anticipated to be bought, resulting in annual spending exceeding $25 billion. However, if an estimated 28-68% of patients struggle with proper inhaler use, the loss could range from $7-15.7 billion, providing little benefit to patients or the healthcare system. Furthermore, the effect on patients who mistakenly believe they are using their inhalers correctly is more distressing than the financial loss.

They continue to experience dyspnea, discomfort, morbidity, and death as a result of their uncontrolled or ineffectively treated airway condition. As a result of the patient's misunderstanding, the healthcare provider becomes frustrated and continues to raise the dosage to get a result above the therapeutic threshold, adding to increased expense and wasted medicine. This inability to alleviate signs and symptoms leads to the more unplanned clinic, emergency department, and hospital visits, resulting in a significant loss of total productivity due to lost school or work days. The loss is expected to be in the billions of dollars [39].

MEASURES TO OVERCOME

Understanding the obstacles that may limit the successful use of inhalers is the first step in overcoming such challenges, which is then followed by the prescriber's selection of the most effective device for the specific patient [41, 42], as well as patient education and training for device usage. A monitoring mechanism, as well as training, should be in place to keep the patient's skills in check.

The patient's desire, the patient's and health practitioner's knowledge of the device, the capability to use it accurately, the convenience and portability of the device, and the availability of the device are all variables to consider when selecting an inhaler [43].

Education and training

Training can be given to an individual patient, but group training is much more effective. The ease of access to printed or electronic material during training allows patients to use it as extra assistance.

Patients should be provided inhalers based solely on their understanding of the devices. According to scientific evidence, dealing with and using particular inhaler devices is easier than others. When compared to the Handi-Haler, it required substantially less time to remove mistakes in inhaler usage with the Diskus [44]. If, after sufficient instruction, patients continue to use bad techniques with a certain device, moving to another device that is likely to solve the challenges is the best course of action.

A variety of resources are available to help people and healthcare providers learn how to use inhalers. For example:

• Tools like 2Tone Trainer ("Canday Medical Ltd, Newmarket, UK"), Diskus/Accuhaler Training Device (Vitalograph, Ennis, Ireland), TurbuHaler Trainer (AstraZeneca, Lund, Sweden), and the In-Check DIAL inspiratory flow meter ("Clement Clarke International Ltd, Harlow, UK"), could be utilized to assess a physical capacity of patient to utilize a certain inhaler [45].

• The introduction of electronic monitoring devices, like Adherium Ltd's SmartMat, SmartTurbo, and SmartTrack (all created in Auckland, New Zealand), could give objective and thorough adherence data to help clinical decision-making [46].

Utilization of Inhalation Aids

A variety of inhalation aids have been introduced in classic MDIs to resolve coordination challenges and to improve aerosol deposition within lower airways, and other types of inhalers have emerged. They are referred to as "spacers" and are classified into 3 types: (1) collapsible bags, (2) reservoirs or tubes with valves, and (3) tubes without valves [47,48,49].

Before it reaches the mouth, spacers gradually slow down the aerosol spray, allowing the propellants to burn out and big particles to settle out of the cloud. This results in reduced deposition within the oropharynx as well as intrathoracic airways [47]. Spacers could also eliminate the necessity for synchronization between aerosol discharge and inhalation [47].

Inhaler treatment innovations include not just the creation and refinement of current technologies, but also encompass the development and improvement of existing technologies; such as the inclusion of dosage counters or extending patent insurance to pediatrics. To enhance the patient's experience, dose counters were added to the "TEVA QVAR® range" [50].

CONCLUSION

To summarize, the same accessibility that makes it simpler the respiratory system an obvious target for pathogens also makes it simpler to cure. As a result, inhalation therapy is at the forefront of pulmonary illness treatment. In this article, we covered pMDIs and DPIs, which transport the medicine directly to the site of action and are therefore efficacious. pMDIs need hand-breath coordination, whereas DPIs result in reduced medication delivery to the lungs if exhaled into the device. These medicines, while relatively simple, have intrinsic obstacles to effective medication administration by patients that, if not solved by teaching and training patients on inhaler usage, may result in significant cost loss.

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