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Inhalation devices for asthma and COPD: A review of the literature

Dispositivos de inhalación para asma y EPOC: una revisión de la literatura

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Abstract

Recent research on asthma and COPD has concentrated in developing new inhalation delivery systems. Innovation has improved metered-dose, dry-powder, or breathe-actuated inhalers and nebulizers. The objective of this study was to review current literature on the different inhalation devices available in the market, and how their characteristics have associations with disease outcomes both for asthma and COPD. The main concerns have been to facilitate the drug's administration for the patient, as measured by pharmacokinetics, safety, patient preference, medication adherence, quality of life, and costs. Medication adherence has a positive association with patient preference and ease of use of the device that administers the drugs for disease control. A good medication adherence can reduce exacerbation episodes, improving QOL, and reducing costs for respiratory diseases.

Keywords: Nebulizers and Vaporizers, Biological Availability, Patient Safety, Medication Adherence, Patient Preference, Quality of Life, Review.

Resumen

Las investigaciones recientes se han concentrado en el desarrollo de nuevos dispositivos de inhalación. La innovación ha mejorado los inhaladores de dosis medida, polvo seco o respiración controlada y los nebulizadores. El objetivo de este estudio fue realizar una revisión narrativa de la literatura acerca de los diferentes dispositivos de inhalación que se encuentran disponibles en el mercado y su asociación con los desenlaces para asma y EPOC. Las principales preocupaciones han sido facilitar la administración del medicamento al paciente favoreciendo la farmacocinética, seguridad, preferencia del paciente, cumplimiento de la medicación, calidad de vida y costos. La adherencia a la medicación tiene una asociación positiva con la preferencia del paciente y la facilidad de uso del dispositivo que administra los medicamentos para el control de la enfermedad. Una buena adherencia a los medicamentos puede reducir los episodios de exacerbación, mejorar la calidad de vida y reducir los costos de las enfermedades respiratorias.

Palabras clave: nebulizadores y vaporizadores, disponibilidad biológica, seguridad del paciente, cumplimiento de la medicación, prioridad del paciente, calidad de vida, revisión.

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Introduction

Research on medical devices has been growing steadily, particularly in areas where non-oral self-administration is involved, as is the case for subcutaneous injection of insulin (1) or inhalation of drugs for asthma and other pulmonary diseases. A search in the biomedical database PubMed shows how publications with the MeSH Term "nebulizers and vaporizers" have increased over the years (**Figure 1**), with a current average of more than one publication per day.

Inhaled medications have been developed for different conditions (2). Inhalators were first used for asthma and COPD control, but new indications have arisen, like insulin for diabetic patients, or antibiotics to treat infections in cystic fibrosis (2, 3). The advantages of inhalation include a faster onset of drug action, lower doses of the medication, and less systemic side effects (4). While new inhaled molecules are being studied, most of the research has concentrated in developing new delivery systems (3, 5). Innovation has improved metered-dose, dry-powder, or breathe-actuated inhalers and nebulizers (4, 6). The main concerns have been to improve pharmacokinetics, safety, patient preference, medication adherence, quality of life, and overall costs.

Biological availability

Four essential variables should be considered in inhalers for asthma therapy: lung deposition and retention, bioavailability, disease state and age of the patient (3). Lung deposition and retention is related with variability in drug dosing, and depends on inhalation technique and on the inhaler device itself (3, 7). Pulmonary metabolism and mucociliary clearance are related with disease state and with age, and may influence bioavailability. Drug waste, when it is either ingested or remains in the inhaler's mouthpiece, is another important variable. For the drug to reach its receptor target, high pulmonary with low oral bioavailability are required in order to reduce adverse effects (2, 3, 7, 8). Patient age and disease severity may require different inhaler formulation properties, as may be the case in both pediatric or geriatric asthma (3, 7).

There is no easy way to assess local lung concentration directly, so pharmacokinetic and pharmacody-

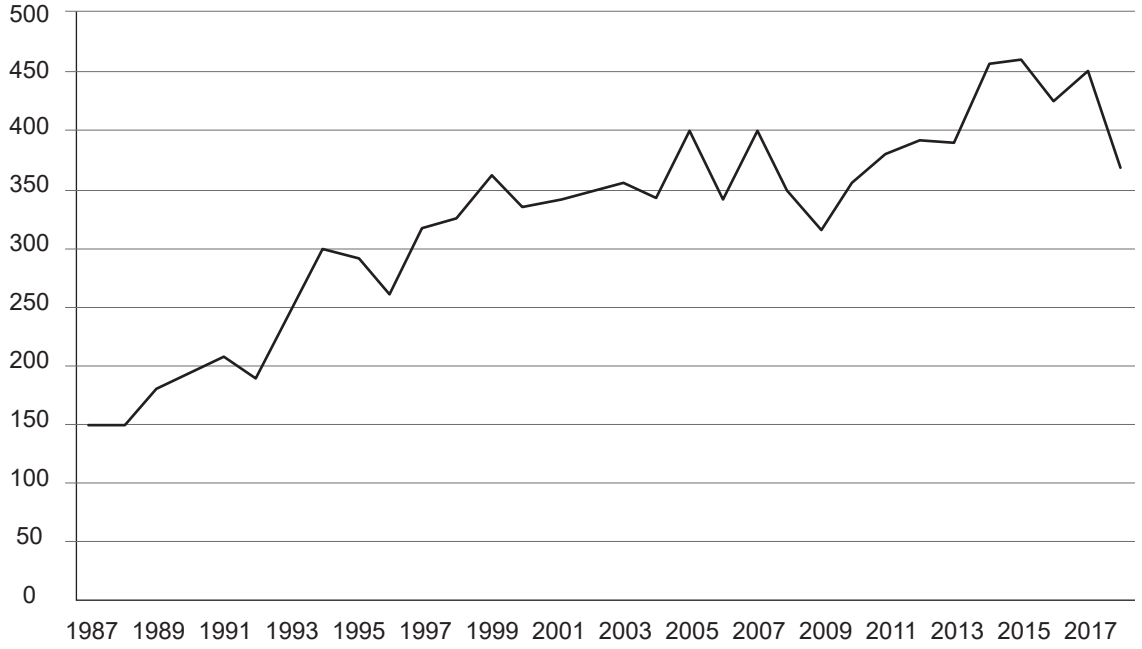


Figure 1. Publications containing "nebulizers and vaporizers" as MeSH term.

namic models are required (8, 9). These help interpret clinical outcome parameters, and assist either during early clinical development or when switching a device or formulation in a non-respondent patient (3, 8). The effectiveness of an inhaler depends on its inherent characteristics, but also on the inhalation maneuver performed by the patient (10). Three steps can describe the inhalation process: 1) dose delivery from the inhaler; 2) proportion of the delivered dose that reaches the target; and 3) functional response to the deposited dose. The first step is influenced by the patient's handling of the device, as well as by the inhalation flow used. The second step is influenced by factors such as coordination in the inhalation, psychological and neurological conditions from the user, or airway flow restriction due to airway closure, or amount of mucus. Finally, the third step involves medication potency, partial agonistic activity, or the possibility of irritation or paradoxical effect, with bronchoconstriction (9-11). All these variables lead to consider both the drug or drug combination required, but also the appropriate individualized device to optimize its effect (9, 11, 12). Several studies, including in vitro models (8), show a relationship between the amount of drug deposited in the airway and its clinical effects (3, 8, 11).

Patient safety

Both clinical efficacy and safety are essential properties when choosing inhaled medications (12). To reduce inhaler-related side effects, the ideal device should be easy to use, dose delivery should be independent of the inspiratory flow, and release of the aerosol should be slow and constant, favoring low oropharyngeal and high pulmonary deposition (13).

One safety issue is cardiovascular response, determined by measuring heart and respiratory rate or blood pressure, before and after administration. Other adverse effects include cough, nausea, vomiting, palpitations, and tremors (4). Most of the inhalation agents (β2 agonists, or inhaled corticosteroids like fluticasone and beclomethasone) have good safety profiles and are well tolerated, with few serious adverse events and no deaths reported. Most serious adverse effects are related to patient comorbidities (14-16). Chronic use of inhaled corticosteroids in children with mild or severe asthma has been associated with growth suppression; and evening dosing, in particular, could reduce nocturnal growth hormone activity (12, 17, 18). Even mild side effects could influence adherence and, in the long run, reduce effectiveness (3).

Medication adherence

Poor adherence is a major issue in chronic disease treatments, and is common in patients with inhaled regimens (6, 18). Both improvements in device design or combinations of two drugs in a single device may lead to better adherence (6). The most common devices used for respiratory drug delivery are pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers. In general, pMDIs are convenient due to their portability, ease to maintain, multiple dose capacity and effort-independent characteristics. pMDIs present issues related to the administration steps done by the patient, which require coordination and breath-holding. These issues may lead to ineffective doses delivered to the patient. On the other hand, DPIs are less reliant on coordination and breath-holding; dose delivery depends on patient's inspiratory flow. This is why DPIs are not suitable for patients who are unable to generate sufficient airflow, such as children, the elderly or patients with severe asthma or COPD. Nebulizers are able to deliver effective doses irrespective of breathing flow or pattern, an advantage for patients who are not able to use pMDIs or DPIs. Some disadvantages from nebulizers are the frequent cleaning they require, and longer treatment times, drug wastage, and large size (6, 19). In an adherence assessment study performed in the Netherlands, adherence was related to the device that the patient was using, since some devices may be more difficult to use than others (20). New technological devices place emphasis on making inhalation administration easier for patients (21). The issue is important, since low adherence has been associated with poor disease control, higher morbidity, increased number of hospitalizations, and higher mortality rate (22, 23). Many strategies can be implemented to increase medication adherence, for example education programs, audiovisual feedback, electronic reminders, and increasing the number of patient-physician encounters (24-27). Evidence suggests that educational intervention are perhaps the

most effective (28-30). It is essential to individualize each patient and focus on particular reasons for potential non-adherence (30). In a study performed in Spain, specialists recognize selection of inhalation devices as a strategic therapeutic decision, which should be based on the characteristics of each patient, since some devices may be more suitable according to each patient's profile (31).

Even if patients have a good adherence to their treatment, poor compliance to device technique can result in poor outcomes. Patients perform multiple mistakes when handling an inhaler (32, 33). In a study performed in nine countries (Brazil, Canada, France, Germany, Italy, Japan, the Netherlands, UK and USA) a Real-life Experience and Accuracy of inhaler use (REAL) survey was applied to 764 patients, and identified characteristics that influence optimal inhaler use and adherence. They evaluated five different features: confidence in taking full dose, self-reported adherence, ease of use, training received, and medication effectiveness, and found a negative association between inhalation mistakes and disease control (34). Another study which enrolled 1164 patients with both asthma and COPD, evaluated inhalation technique, and found that the most common mistakes were not shaking the inhaler (for suspensions), not exhaling fully before inhalation, inhaling too forcefully and not holding breath for enough time after inhalation. This mistakes lead to more episodes of exacerbation and to higher treatment cost (33).

According to one study, nearly 94% of patients with asthma and COPD do not use their inhaler correctly (19). Inhalation errors can be divided into simple and critical. Simple errors decrease clinical efficacy of a given inhaler, while critical errors make inhalation clinically ineffective (35). Various methods can be used to reduce inhaler administration mistakes. Training and education about the device is one of the simplest solutions, and has shown to increase medication adherence and better control for asthma; this instruction should be repeated on a regular basis in order to be effective (27, 32, 36). In a study by Takemura et al. (36), in Japan, a cross-sectional analysis was performed using a self-reported adherence test in 55 patients, and the only significant factor associated with overall adherence was receiving repeated instruction ($p = 0.032$); 22 patients received repeated verbal instructions and demonstrations of inhalation technique by a respiratory physician, and significant correlations were found between overall mean adherence scores and health-related quality of life score (St George's Respiratory Questionnaire: total $r = -0.35$, $p = 0.023$; symptoms, $r = -0.43$, $p = 0.002$; impacts, $r = -0.35$, $p = 0.011$). Another solution is using devices that involve normal tidal breathing, which provides the ability to achieve efficient drug delivery to patients unable to perform inhalation maneuvers correctly, and coordinate their breathing for appropriate inspiratory flows (6).

Patient preference

Several recent innovations have improved the efficacy and performance of inhaler devices. Along with technological progress, and ideally with a once-daily dosing, it is important for patients to acquire the ability to use devices properly (13). However, in an online survey applied to 245 COPD patients, fewer steps to operate the inhaler, confirmation that the dose had been taken correctly, and easy coordination of the breathing maneuver were considered more important to patients (37). Simplicity is one of the most important features from a patient perspective (38). A study in Australia, with 25 patients, showed that pMDI users perceived that their devices were easy to use, while DPIs users reported that loading each dose was a troublesome step, followed by concerns about inhaling the appropriate dose during an attack. Patients also felt that smaller-sized inhalers are linked to improved adherence due to their portability, and had concerns about pMDIs hygiene, since lids can acquire dust or other particles more easily, and could potentially aggravate asthma during inhalation (19). A study performed by Hawken et al. (39) in the Netherlands, with 201 patients with asthma and 93 with COPD, stated that similar preferences were reported for both diseases, and patients would be willing to change their inhaler if they were offered the option of a new one with improved characteristics.

On the other hand, physicians seem to have no particular preference for a specific device, and place more importance on ease of use when selecting inhalers for the elderly, or people with more severe stages of the

disease, particularly in COPD (38). For the elderly special considerations must be taken into account, such as cognitive function, hand strength and manual dexterity when selecting an inhaler device (40). Inhaled medications for asthma and COPD are available in different devices, and it is important to consider the patient perspective as part of treatment and device selection, since this could differ from the physician perspective. Patient preference has a positive relationship with medication adherence. Important features for a device are intuitiveness and to ensure that the correct inhaler technique is applied, with limited number of steps (39, 41).

Quality of life

Any medical treatment should ideally improve quality of life (QOL) and, except when adverse effects predominate, better medication adherence should also lead to this objective (36, 42). Patients with low adherence are more likely to experience disruption of their daily-life activities, due to loss of work or school days (6). In a study performed in Thailand with 400 patients with asthma, 44% had missed work or school due to exacerbation episodes (43). In another cross-sectional Indian study with 330 patients with asthma, uncontrolled disease was the main factor associated with low QOL. Common causes for uncontrolled asthma include incorrect inhaler technique in up to 80% of patients, as well as low adherence; proper technique of inhaler use improves QOL and other clinical outcomes (44). Severity of the disease, of course, is also correlated with QOL (45, 46).

In a study of QOL in 69 COPD patients (42), a planned inhaler training reduced exacerbation and dyspnea episodes, improving QOL. Another study performed in Serbia with 312 patients with asthma or COPD evaluated their inhalation technique and stated that adherence to therapy is a key factor for a successful treatment. This is why health care professionals should insist on educational programs aimed to improve patient's inhalation technique with different devices, resulting in long-term disease control and better QOL (47). On the other hand, QOL is associated with costs. An economic evaluation performed by Earnshaw et al. (48) showed that treatment of COPD with salmeterol/fluticasone reduces number of exacerbations, and was cost-effective (less than $50,000 USD per QALY gained) compared with no maintenance. Overall, the literature reviewed suggests that ease of use of an inhaler will have a positive effect on effectiveness and safety, on medication adherence, on clinical outcomes, and on QOL.

Device comparison

Synchrobreathe®

The Synchrobreathe® device is powered by the patient's inspiration and has been comparable to conventional volume spacers, improving the relative pulmonary bioavailability systemically for fluticasone/salmeterol (49, 50). This device by Cipla®, is a new generation of breath-actuated inhalers (BAI) with an integrated dose counter that combines features from both DPIs and pMDIs; it also has a soft-triggering mechanism that is actuated at a lower respiratory rate that almost every patient can generate, overcoming issues regarding optimal drug deposition (51). BAI facilitate the inhalation technique because no coordination is needed; also, these devices are portable and compact, which is an advantage related to patient preference. However, one disadvantage is that in case of severe stages of disease and exacerbation episodes, the inspiratory flow needed for the medication to be triggered could not be enough (52-54). It is important to highlight that the Synchrobreathe® device requires the lowest inspiratory flow compared to all other devices available in the market. In an open-label, prospective study performed by Balamurugan et al. (53), 421 patients with asthma and COPD were assessed for device handling, ease of use and perception regarding Synchrobreathe® vs pMDI. These patients were also evaluated for the ability to use the device without errors at the first attempt, patient preference, total number of training sessions, and number of attempts to perform correct technique on day 1 and day 14. The number of participants who did not make any mistakes after reading the patient information leaflet was low (23%; $p<0.05$), but on day 14 more patients used Synchrobreathe® correctly (68.2%; $p<0.01$). The total number of mistakes before (2.1 ± 1.3; $p<0.001$) and after training (2.8 ± 0.2; $p<0.001$) was significantly less com-

pared with pMDI (3.5±0.2). The average time required to perform the inhalation technique correctly ($p < 0.01$) and the number of attempts to inhale correctly was significantly less ($p < 0.001$) with Synchrobreathe® on day 1 and 14. Most of participants chose Synchrobreathe® over the pMDIs alternative.

Respimat®

Respimat® is a soft-mist inhaler (SMI), propellant-free, multi-dose by Boehringer Ingelheim®, which produces an aerosol cloud with droplets in a small particle mass (13). It also increases lung deposition and reduces oropharyngeal deposition of the drug, comparing it with pMDIs and DPIs, without the use of spacer devices (52, 54). Additionally, the long generation time of the aerosol cloud (approximately 1.5 seconds) facilitates coordination of inhalation and actuation generating higher lung deposition, which is a major problem with pMDIs (55). Because of this characteristic this device does not need a high inspiratory flow, when the patient is given appropriate instruction, and are taught that lower inspiratory flows are optimal (56). Clinical trials have shown that medication delivered by Respimat® is effective and requires smaller doses in patients with obstructive airway diseases (57). One of the main disadvantages regarding this device is its cost, which has an economic impact for patients and for the health care system (52). A review by Hodder et al. (58), using objective and validated patient satisfaction instruments, showed that Respimat® was well accepted, especially in COPD patients because of its handling and inhalation characteristics. This device was compared with pMDIs and Turbuhaler® showing higher clinical and patient satisfaction.

Ellipta®

This is a multidose DPI device with blisters by GlaxoSmithKline®. Its aerolization is affected by inspiratory flow generated by the patient, which is ideal for patients with low inspiration airflow (35). This device generates aerosols with better parameters, independent from the patient's inspiratory flow, turning it into a more patient-friendly device. Its use requires three steps: 1) slide a cover down until hearing a click; 2) inhale the medicine; 3) slide the cover up and cover the mouthpiece; these decrease the risk of inhalation mistakes compared to other DPIs available in the market (59). Advantages of this device are its portability and compact use, and its breath actuated action, which does not require coordination, and propellant free characteristics. Ellipta® requires more than 30 L/min to trigger the medication (56), which could be an issue during exacerbation episodes or advanced stages of disease (51). A study from the Netherlands, with 567 patients with COPD and 162 with asthma, assessed the proportion of patients that made critical and overall mistakes using Ellipta® and other commonly used inhaler devices such as Diskus®, metered dose inhalers (MDI), Turbuhaler® and Breezhaler®. Fewer asthma and COPD patients made critical mistakes with Ellipta® after reading the patient information leaflet vs Diskus® (3/70; 4% vs 9/70; 13%; $p = 0.221$), vs MDI (2/32; 6% vs 8/32; 25%; $p = 0.074$), and even fewer vs Turbuhaler® (3/60; 5% vs 20/60; 33%; $p < 0.001$). Also, more patients preferred Ellipta® over other inhalers because of its ease of use compared with Diskus® (97% vs 60%), MDI (92% vs 44%), and Turbuhaler® (96% vs 55%), all with $p<0.001$. These results were obtained across most of the criteria in the preference questionnaire, except for the size of the inhaler and comfort of the mouthpiece, which was similar between the devices (60).

Diskus®

This is a multidose device by GlaxoSmithKline® that uses s strip foil containing blisters and is classified as a DPI. It provides medication for up to one month (52). The steps involved for this device are: 1) expose the mouth piece, hold the Diskus® horizontal in one hand and with the other load the dose, a click must be heard; 2) push the lever to prepare the dose, hold the inhaler flat and level, another click has to be heard; 3) inhale the medicine, and 4) close the inhaler (35). An average of 50% of patients use DPIs incorrectly, with the most common mistake being failure or difficulty in loading the device before inhalation and exhaling into the device (61). Because of the difficulty performing self-administration steps, Ellipta® has replaced this device (62). Despite its low intrinsic resistance; it does not have a triggering mechanism, which makes drug delivery entirely dependent on the patient's inspiratory

maneuver. Also, employing drug blisters can cause incomplete emptying of the metered dose, reducing the amount of drug delivered to the lung, consequently reducing clinical efficacy (52). As Ellipta®, this device requires an inspiratory flow higher than 30 L/min to be triggered (56), which could be a disadvantage in certain patients, when compared to other devices. In a review performed by Ninane et al. (13) several randomized controlled trials indicate that patients tend to prefer newer and easier to use devices, finding that Diskus® was preferred by patients before Ellipta® was released to the market.

Turbuhaler®

This is a multidose DPI by AstraZeneca® that measures remaining doses from a powder reservoir. This type of device produces a fair lung deposition with sufficient (about 60 L/min) inspiratory flow (52). As Diskus®, this device does not have a triggering mechanism, making it entirely dependent on the quality of the patient's inspiration maneuver requiring an inspiratory flow of approximately 60 L/min (52, 56) which is twice the inspiratory flow needed for the Synchrobreathe® device. There are many variations in the design and performance of different types of DPIs, and patients do not use them equally well, making DPIs not easily interchangeable (47, 63). The steps for its use are: 1) unscrew the cover; 2) load dose by holding the inhaler upright, turn the grip dial as far as it will go in one direction, then turn it back to its original position. A click must be heard; 3) inhale the medicine; 4) replace the cover and close (35). Older DPIs such as Diskus® and Turbuhaler® have a higher number of steps that make them more challenging for self-administration (35). In a study, approximately 80% of patients were unable to use Turbuhaler® correctly (61). One of the common mistakes is the failure to turn the base fully in both directions and to keep the device upright until loaded (52). In addition, Turbuhaler® has a high intrinsic resistance, making it difficult to generate an optimal inspiratory flow to release the drug particles. This is an issue in children and the elderly, who might have airflow limitations (61). In a large randomized trial using long-acting β2 in patients with mild to moderate asthma, two inhaler devices, Diskus® and pMDI were compared to Turbuhaler®. After 8 weeks, similar improvements of morning PEF were found for all treatment groups. There was also a 4-week blinded-treatment period, in which patients preferred Turbuhaler® to pMDI. No differences were found with other comparisons made in this study (64).

Breezhaler®

Breezhaler® by Novartis® is a capsule-based DPI developed to improve functionality and intuitiveness over a previous device called Aerolizer®. Its main advantage is once-daily dosing (13). This device has similar steps to Turbuhaler®, and in a study with 165 patients with asthma and COPD, both devices had more incorrect applications compared with Diskus® or Ellipta® (28). Breezhaler® requires an inspiratory flow greater than 50 L/min for the powder dispersion (56). This is higher than the inspiratory flow rated needed to action the Synchrobreathe device. In a study which evaluated factors associated with appropriate inhaler use in COPD in nine countries, Breezhaler®, Ellipta®, Respimat®, and Genuair® were compared. Patients reported highest inhaler treatment adherence in the last 30 days with Breezhaler® (90%, n = 186), followed by Respimat® (70%, n = 20), Ellipta® (65%, n = 191) and Genuair® (58%, n = 194). Also, more patients felt confident or very confident of having taken their full dose of medication with Breezhaler® (93%) vs patients using Ellipta® (80%, p = 0.001) or Respimat® (76%, p = 0.001) (34). In another study from Brazil (65) 140 patients were randomized, 136 received at least one dose of Breezhaler® and 135 of Respimat®. When treatment started the rate of correct inhaler use was 40.4% (95% CI: 32.2%-48.7%) for Breezhaler® and 36.3% (95% CI: 28.2%-44.4%) for Respimat® (p = 0.451). After 7 days, rates were 68.9% (95% CI: 61.1%-76.7%) and 60.4% (95% CI: 52.2%-68.7%) respectively (p = 0.077). According to a satisfaction questionnaire performed for this study, patients were more satisfied using Breezhaler® (57.1%; p = 0.001) than Respimat® (30.1%; p <0.001).

Cost of illness

A study that included 20,410 patients from an administrative database in Colombia estimated the mean annual cost for mild (USD $335, SD 1,489), moderate

(USD $498, SD 1,940), and severe persistent (USD $865, SD 2,050) asthma for 2015. As expected, they concluded that health care services utilization and direct costs for asthma were related to disease severity (66). On the other hand a study from 2007 estimated annual costs of COPD: $2,088 USD for mild COPD, $2,853 for moderate COPD and $9,229 for severe COPD (67).

A cost-utility study of an educational intervention to reduce critical handling error because of insufficient inspiratory effort demonstrated that direct cost savings could be achieved. These savings were £45/£86 with 0.0053/0.0102 additional QALYs, and the highest probability of being cost-effective at a £20,000/QALY threshold (68). With this it could be inferred that an efficient device should save costs due to its ease of use and critical error handling reduction. Another study estimated economic burden of poor inhalation techniques for asthma and COPD in three European countries. Lewis et al. concluded that the direct cost burden of managing these two respiratory diseases for patients using Turbuhaler® or Accuhaler® in 2015 was estimated at €813 million, €560 million, and €774 million for Spain, Sweden and the UK, respectively. Poor inhalation technique represented 2.2%-7.7% of direct costs, for a total of €105 million across the three countries, which is not a negligible amount (69). By making it easier to perform inhalation techniques for patients, these costs could be reduced.

A Delphi consensus statement, a technique that has been widely used to estimate economic variables when uncertainty prevails (70) was performed by Ninane et al. (71) in which most experts (54%) did not agree with the idea that physicians should prescribe the least costly inhalation devices for the community, and most (94%) disagreed with the statement that pharmacists should deliver the least costly inhaler devices, even if the device contained the same active substance prescribed by the physician.

In summary, there is solid evidence to support the fact that, apart from the medication used, inhalers play an important role in the control of respiratory diseases like asthma and COPD. Differences explored include bioavailability of the drug, efficacy and safety issues, as well as ease of use, all of which influence patient adherence and preference. Innovation in new inhalers has led to better disease control which has been proved to correlate with QOL, less resources required by health providers and overall cost reductions to the health system.

Conclusions

- An ideal inhaler device should have positive effects among bioavailability, safety, patient preference, medication adherence and QOL at a reasonable cost.
- Medication adherence correlates with patient preference and with ease of use of the device.
- Good medication adherence can reduce exacerbations, improve QOL and reduce costs for respiratory diseases management.
- Devices which require low inspiratory flow for optimal drug delivery should benefit children, the elderly, and other adult patients with obstructive airways diseases.
- An appropriate device selection could reduce disease medical costs related with emergency and outpatient visits, as well as hospitalizations.
- More research is needed regarding the possible advantages of Synchrobreathe® device, specifically comparing it with other inhaler devices available in the market, but this novel breath-actuated inhaler can address key issues arising during the use of both pMDI (hand-breath coordination) and DPIs (high inspiratory flow required) for optimal drug deposition.

Conflicts of interest

This review was financed by Cipla®, the manufacturer of Synchrobreathe®. MRM declares no additional conflicts of interest. DR has received research funds and has lectured for AstraZeneca®, manufacturer of Turbuhaler®; Boehringer Ingelheim®, manufacturer of Respimat®; GlaxoSmithKline®, manufacturer of Ellipta® and Diskus®; and Novartis®, manufacturer of Breezhaler®.

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