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Dry powder inhalers — between the doctor and the patient

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Abstract

The article briefly presents currently accessible dry powder inhalers (DPI). Basing on the data from the literature, we discussed the most common mistakes related to the utilisation of DPI as well as their clinical and economic consequences. We also extensively analysed all factors that may influence the efficacy and safety of inhaler therapy of asthma and COPD, mostly with the use of DPI. In addition, we indicated the potential to improve the efficacy of inhaler therapy from the doctor and COPD or asthma patient perspective. We also presented a DPI choice algorithm including the patient's preferences and competences.

Key worlds: dry powder inhaler, asthma, COPD, patient, errors in inhalation

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Introduction

The article aims to discuss the factors which influence the correct use of a dry powder inhaler (DPI). A special emphasis has been put on the elements depending on the doctor and on the patient. We made a survey of the most important publications from the last 15 years, accessible in the PubMed database, which concern the technique of inhalation with DPI, errors made by patients with asthma or chronic obstructive pulmonary disease who use that type of inhalers as well as the rules of a right DPI choice.

Dry powder inhalers — today and yesterday

Medical aerosols are biphasic dispersed preparations. In case when a colloid is formed by liquid droplets dispersed in gas medium, it is called a liquid aerosol. If the dispersed phase is set up with solid particles, it is called a solid (powder) aerosol [1]. The dry powder aerosols are produced by dispersion in the air of the previously appropriately developed (micronised and measured out) dose of the powdered drug. That is why these devices are called dry powder inhalers [2] and are the most numerous and highly technically diversified (construction and mechanism of action) group of inhaler devices [3, 4]. The Figure 1 presents the categories of DPI based on the type of the aerosolization of the powder and on the preparation of the drug dose. The examples of DPI present on the Polish market are also included.

In the passive DPI patients inspiration is used to disaggregate the powder molecules and to change them into aerosol. The acceleration during the initial phase of the inspiration, the amount of the peak inspiratory flow (PIF), time to reach a PIF, the respiratory capacity and the duration of the expiration are crucial for the process [5, 6]. The necessity to take an appropriately forced, deep and long inspiration limits the accessibility of these type of DPI to patients incapable of performing this inspiratory manoeuvre [4]. As a rule,

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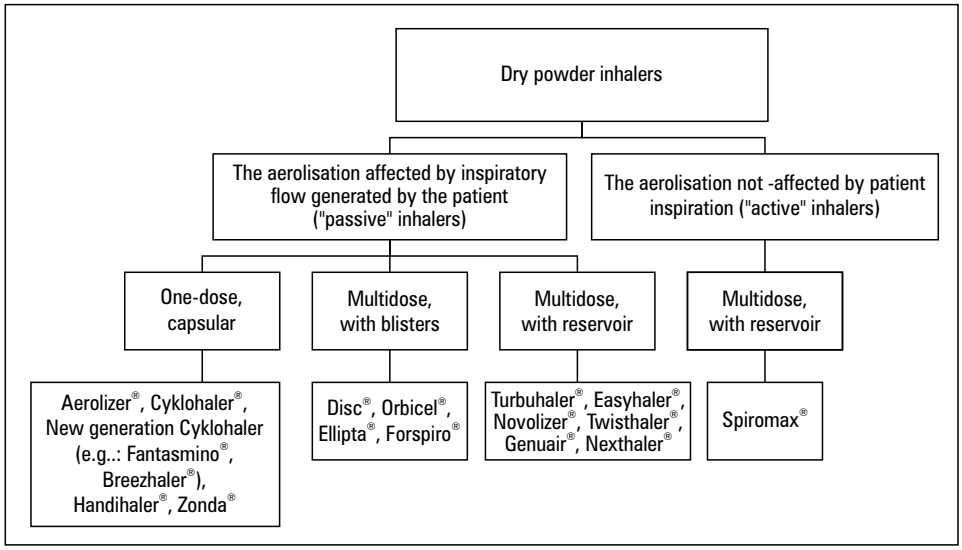

Figure 1. Types of dry powder inhalers

these are elderly people with muscles weakened by the chronic disease process, persons with psychiatric and /or neurologic disorders as well as children under 6 years of age . In these groups of patients, there is a high risk of not generating the optimal inspiratory flow. And only the optimal inspiratory flow guarantees the appropriate process of disaggregation and aerosolisation of the powder, an optimal penetration and deposition of such an aerosol in the respiratory tract and, as a result, a clinically effective inhalation [7–13].

In the active DPI, the processes of disaggregation and aerosolisation are independent from patients' inspiration, which makes this type of inhalers easier to use and assures a highly predictable characteristic of the aerosol cloud. A good and, up to the present, the only example of this type of inhaler is Airmax®/Spiromax® [14]. In the past few years some new passive DPI have entered the market (in order of appearing in the market): NEXThaler®, Ellipta®, Forspiro® or Zonda® [15–18]. The new devices usually generate aerosols which have better parameters, normally practically independent from the patient's inspiratory flow but concurrently more patient-friendly in the everyday use compared with the previously appllied devices [19–21]. Ellipta® is a good example of such an inhaler. The implement has replaced a popular for many years Discus® [22]. The construction (blisters inhaler) and the use of this new inhaler (only 3 simple steps) has decreased the risk of inhalation errors, compared with the older types of DPI [21]. The Forspiro® inhaler has similar features, however, it demands 5–6 consecutive actions [17, 23].

How much do the errors in inhalation from DPI cost?

Only the infallibly performed drug inhalation is clinically effective and safe for the patient. The inhalation errors may be divided into simple and critical. The first ones may decrease the clinical efficacy of a given inhaler, and the second ones make the inhalation practically totally clinically ineffective [24]. The DPI inhalation errors are mostly specific to a given type of inhaler but there are also some errors (non-specific), common to all DPI [25]. The most frequent non-specific errors include as follows: not taking a maximally deep expiration (to the level of the functional residual capacity [FRC]) before inhalation, incorrect body position during the inhalation, too slow or too shallow inspiration via the inhaler as well as not holding the breath after the inhalation [26]. The list of the specific errors is much more longer and depends on the type of DPI [25].

The results of the study by Sanchis *et al.* [27] based on the systemic overview of the 144 publications from the years 1965–2014 have shown that over the last 50 years the percentage of patients committing mistakes during the inhalation remains stable , i.e. it oscillates between 45 and 17% [27]. The mistakes in the inhalation therapy concern all types of inhalers (the pressurised metered dose inhalers, DPI, metered dose inhalers (MDI) of a liquid drug, nebulisers), and the percentage of patients depends on the analysed population (patients age, type of the disease, country), type of the inhaler and patients education level. For example, the results of the study by Molimard

Table 1. The percentage of patients with at least one critical mistake made during the inhalation with the most commonly used dry powder inhalers (DPI) in Europe (modification according to [29])

Type of DPI (number of studies)	Percentage of patients and confidence interval
Aerolizer® (n = 4)	14.2% [95% CI 11.0–18.1]
Discus® (n = 9)	20.8% [95% CI 13.7–30.2]
Turbuhaler® (n = 10)	40.1% [95% CI 28.6–52.9]
Handihaler® (n = 3)	42.4% [95% CI 28.8–57.1]

et al. [28] from the year 2003 showed that at least one mistake had been made by 49–54% of patients treated in a standard outpatient clinic/in a medical practice by a general practitioner. Moreover, at least one critical mistake had been made by 11% (Dysk®) to 32% (Turbuhaler®) of treated patients. A systemic review with meta-analysis of the errors made by patients with asthma and COPD in several European countries has been recently published [29]. The authors of the review have proved that the critical mistakes were made during the inhalation, depending on the used DPI, by 14.2–42.2% of patients (on average in 28.4%). The data are shown in Table 1.

The mistakes made by patients with asthma or COPD during the inhalation influence the constitution of the aerosol cloud and the deposition of the rug molecules what has a negative impact on the therapeutic efficacy of the inhaled drugs [30,31]. For example, too weak inspiration (a suboptimal inspirational flow), which is one of the most frequent errors during the inhalation from the DPI, increases significantly the risk of uncontrolled asthma (OR [*odds ratio*] =1.30, 95% CI 0.08–1.57 for Turbuhaler® and OR = 1.56, 95% CI 1.17–2.07 for Discus ®), as well as it increases the risk of asthma exacerbations [25]. In another paper, the authors evidenced that patients who obtained only a suboptimal value of the PIF (for a given DPI) had an higher risk of COPD exacerbation, which demanded admission to the hospital [13]. Other critical mistakes in the inhalation technique with DPI increase almost twice the risk of admission to the emergency room due to a severe intensification of COPD (it concerns 6.9% of patients making mistakes vs. 3.3% in the no mistake group [OR 1.86, 95% CI 1.14–3.04, $p < 0.05$]) [32].

Table 2. Casual medical events induced by inappropriate technique of inhalation [modification according to 33]

Casual medical events	Increase of risk
Admission to a hospital	47%
Visit to an emergency room	62%
Antibiotics therapy	50%
Oral glucocorticosteroids	54%
Medical leave	47%

The errors made during inhaler therapy should therefore increase the costs of therapy of asthma or COPD. Lewis *et al.* [33, 34] analysed the group of patients who were using inhaled glucocorticosteroids (GCS) and long-acting beta-2 agonists (LABA) with the popular DPI: Turbuhaler® (budesonide + formoterol) or with Accuhaler® (Disc) (fluticasone propionate + salmeterol) for one year in several European countries. The study published in the year 2016 supplied many practical conclusions [33]. Firstly, it was showed that the inappropriate technique of inhalation with the DPI significantly increases the risk of hospitalisation, visits to the emergency room, antibiotic therapy or the use of oral GCS (by 47%, 62%, 50% and 54% respectively) (Table 2).

Secondly, 5.4–20.7% of casual medical events and cost have been related to the incorrect technic of inhalation. Thirdly, additional direct costs increase the total therapy price per patient contingent on incorrect inhalation technique to 271 Euros per year in Spain, 466 Euros per year in Sweden and 506 Euros per year in the United Kingdom (data from 2014). Fourthly, the incorrect inhalation technique constituted 2.2-7.7% of direct expenses that generated an amount of 782 million of Euros, considering the total cost of asthma/COPD management in these 3 countries which equalled 5.5 billion of Euros (data from 2014). The similar data for Poland are missing but we should expect comparable proportions of costs. The same team of authors also proved that the change of the passive DPI to an active DP (easer inhalation for the patient) reduces the number of mistakes and improves the inhalation technique, which results in better control of the disease and generates substantial savings, mostly due to the reduction of the adverse medical events [34].

Factors influencing the efficacy and safety of inhaler therapy

The scheme of factors which determine the efficacy and safety of inhaler therapy are shown

in Figure 2. It is known since many years that it depends on the 5 following equally important factors: physician, drug, inhaler, educator and patient. These 5 elements are mutually related, which finally forms the correctness of the patient inhalation technique and his compliance. These two elements determine efficacy, safety and satisfaction of the patient from the recommended inhalation therapy. The five factors are also influenced by the health care system in a given country, including such elements like: way of organisation of the health care system, rules and reimbursement rate of the inhalation drugs, access to specialists and health educators (in Poland usually a physician or a nurse are at the same time health educators)

The most important physician and patient dependant elements related to the DPI are presented in Figure 3.

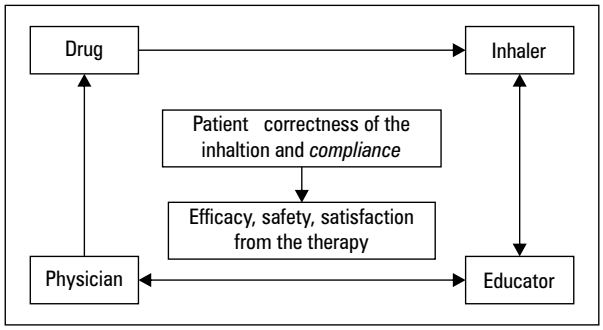

Figure 2. The elements which influence the correctness of the inhalation technique of the patient and his compliance as well as the efficacy, safety and satisfaction of the patient from the recommended inhalation therapy

How to improve the effectiveness of inhalation therapy — physician's perspective

A physician is a person that initiate the primary choice of the inhalation drug and then the selection of a particular inhaler containing a given drug or drugs. To choose a drug, the physician must apply his pathophysiologic knowledge, know the actual therapeutic recommendations in a given disease entity and the accessibility of the drugs on the local market (availability of a drug, its price and reimbursement level). This phase of selection of a drug is relatively easy. A choice of an inhaler containing a selected drug (drugs) is

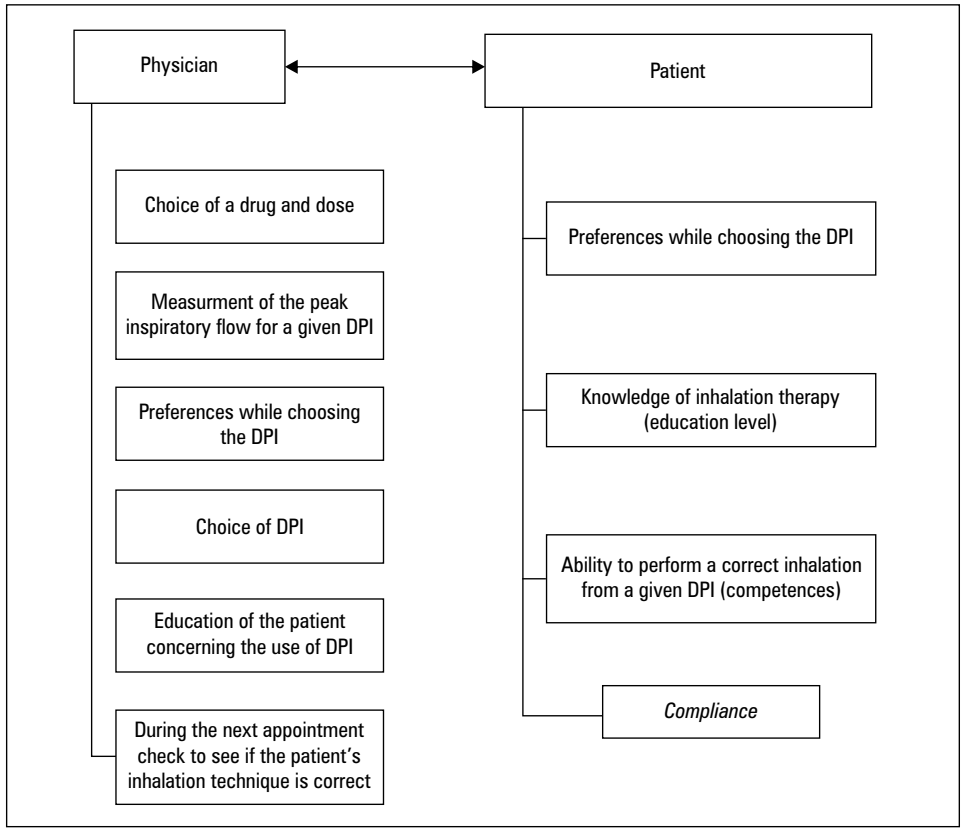

Figure 3. Physician and patient-related factors which determine the correctness of inhalation and patients compliance and, as a result, efficacy, safety and patient's satisfaction from the recommended inhalation therapy with a dry powder inhaler (DPI)

Table 3. Dry powder inhalers (DPI) containing the inhalation drugs used to treat asthma and/or COPD registered in Poland (as of 01.09.2017, in the alphabetic order)

Inhaler/Drug	GCS in	LABA	GCS in + LABA	SABA	LAMA	LAMA + LABA
1. Aerolizer®/Cyklohaler®	+	+	–	–	–	–
2. CNG-Breezhaler®	–	+	–	–	+	–
3. CNG-Fantasmino®	+	+	–	–	–	–
4. CNG	–	+	–	–	–	–
5. Dysk®	+	+	+	+	–	–
6. Easyhaler®	+	+	+	+	–	–
7. Ellipta®	–	–	+	–	+	+
8. Forspiro®	–	–	+	–	–	–
9. Genuair®	–	–	–	–	+	–
10. HandiHaler®	–	–	–	–	+	–
11. NEXThaler®	–	–	+	–	–	–
12. Orbicel®	+	–	+	–	–	–
13. Novolizer®	+	+	–	+	–	–
14. Turbuhaler®	+	+	+	–	–	–
15. Twisthaler®	+	–	–	–	–	–
16. Zonda®	–	–	–	–	+	–

CNG — a new generation cyclohaler; GCS in — inhalation glucocorticosteroids; LABA — long-acting beta-2 agonists; LAMA — long-acting muscarinic antagonists; SABA — short-acting beta-2 agonists; Orbicel® — a disc after many technical modernisations (a generic disc)

a next step. To make this choice, the physician must have knowledge concerning the aerosols and the market of inhalers, which changes dynamically in the recent years, also in Poland. This phase is much more difficult and the first errors may by committed, for example the physician may choose a DPI which is familiar to him without including the patient's preferences [35].

In a case the patient is a child, selection of the inhaler is of crucial importance. In children under 5–6 years of age, nebulisers or drugs administered from meter dose inhalers (pMDI) combined with inhalation chamber are used [36]. Dry powder inhalers are devices of first choice in children older than 5–6 years of age and in adults, provided that they are capable of generating the PIF > 30 L/min using a particular DPI [37]. That is why, a consecutive step of selecting an optimal DPI is to test wether the patient can generate the optimal PIF. Some simple medical devices such as: In-Check DIAL, Turbutest, Turbuhaler — whistle or exercise-Disc may be helpful in the process. Some more technically advanced implements which may educate the patient and test the correctness of inhalation with the DPI are also accessible, for example: Vitalograph AIM or Inhalation [38, 39].

Then the physician should identify a patient with high risk of committing a mistake during the inhalation with a DPI. The following persons belong to a high risk group: patients over 60 years of age, with severe obstructive disturbances of the bronchi, with neurological disorders, lonely persons [26, 30]. These people need an appropriate education and a DPI that requires as little as possible (which minimises the risk of committing an error).

It is crucial to prescribe as little inhalers as possible. The optimal approach is to use different drugs in one inhaler, for example from a DPI or a pMDI. This strategy decreases the risk of committing an error during the inhalation and may improve the control of asthma or COPD [40]. A broad range of accessible DPI may impede the implementation of this rule. Poland is a good example of the problem. Currently, 16 different DPI are registered on the Polish market but only 8 of them contain 2 or more drugs used to treat asthma or COPD, and only 8 of them contain a combination of two different drugs (Table 3) [17, 41].

The development of inhalers containing three different drugs may decrease the number of inhalers used by the patient. This strategy of

Table 4. The number and description of steps necessary to perform a correct inhalation with a Ellipta®, Twisthaler®, NEXThaler®, Easyhaler®, Dysk® and Turbuhaler® inhaler (data from Summary of Product Characteristics and from the official patients' instruction manuals of the inhalers) [46–51]

Inhaler	Number of steps	Description and order of steps
Ellipta®	3	1. Slide a cover down, until you hear a 'click' 2. Inhale the medicine 3. Slide the cover up and cover a mouthpiece
Twisthaler®	3	1. Take off (turn off) the inhaler adapter 2. Inhale the medicine 3. Put the adapter in place, screw it clockwise and press gently until you hear a 'click'
NEXThaler®	3	1. Hold the NEXThaler firmly in the upright position and open the cover fully. 2. Inhale the medicine 3. Hold the NEXThaler once again firmly in the upright position and replace the cover over the mouthpiece
Disc®	4	1. Expose the mouthpiece. Hold the Discus horizontal in one hand. With your other hand, put your thumb on the small curved section. Slide it away from you. You should hear a click 2. Push the lever to prepare the dose. Hold the inhaler flat and level with the mouthpiece facing you. Use your finger to slide the lever until you feel it click into place 3. Inhale the medicine 4. Close the inhaler: to close the inhaler put your thumb on the small curved section. Slide it to you. You should hear a click
Turbuhaler®	4	1. Unscrew the cover and lift it off. You may hear a characteristic rattle sound 2. Load a dose by holding the inhaler upright. Turn the grip dial (coloured base portion) as far as it will go in one direction, then turn it back to the original position. The "click" you hear means that the inhaler is ready to use 3. Inhale the medicine 4. Replace the cover and close it tightly
Easyhaler®	5	1. Remove the mouthpiece cap 2. Shake the device up and down 3–5 times, and then hold the device in an upright position 3. Place the inhaler between your index-finger and thumb, press the top of the device once. You will hear a click. Then release it until you hear another click 4. Inhale the medicine 5. Replace the mouthpiece cap

Every DPI has its specific characteristics which may influence patients' preferences. For example, the Ellipta® inhaler is characterised by the following: ease of use (only 3 steps), simplicity of inhalation steps and the shape of the mouthpiece [52]

therapy with aerosols facilitates the education, decreases the risk of mistakes committed by patients and may be a more effective therapy than inhalation with 2–3 different DPI inhalers [42]. The most recent example of the three-drug therapy with a single DPI is a combination of fluticasone furoate with umeclidinium bromide and with vilanterol in the Ellipta® inhaler [43].

The improvement of the efficacy of inhalation therapy seen from the patient's perspective requires as follows: to define the characteristics of inhaler important to a user, to choose a DPI consistent with preferences and possibilities of the patient and to properly educate the patient. The experts suggest that the DPI constructors should really consider patients' opinions and remarks [44]. This suggestion has been considered in the DPI recently introduced onto the market [15, 17]. From the patient point of view, a DPI should be maximally simple to use and should possess the following features:

- As little steps to prepare an inhaler to use, as possible
- Construction that enables to change the order or to skip a step when using an inhaler
- Easy and comfortable process of inhalation
- Possibility to test the correctness of the inhalation
- Visualisation and/or acoustic information about the number of doses left in the inhaler

Modern DPI such as Ellipta®, NEXThaler®, or Twisthaler® have almost all listed above characteristics (Table 4) [15, 45]. In case of older DPI (Dysk®, Turbuhaler®, Easyhaler®), the number of steps is higher and they are more complicated which, has been included in the patients' instruction manuals.

The patient should finally select the inhaler, however, quite often he is not a decision-maker. His preferences concerning the inhaler as well as some predispositions and skills to use the inhaler should be considered. This issue has been empha-

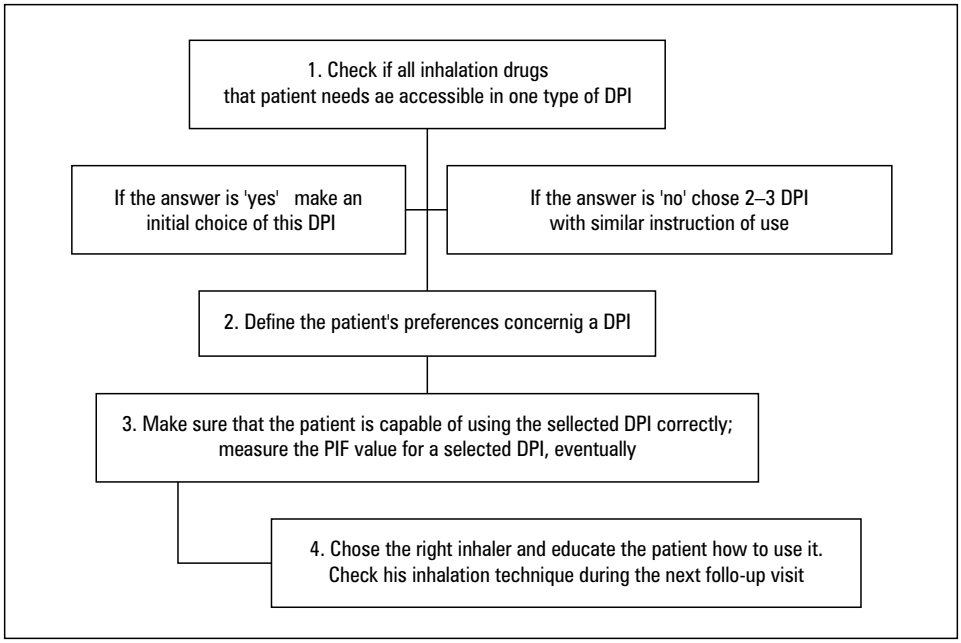

Figure 4. The physician's proceeding scheme to choose a dry powder inhaler (DPI)

sised since several years in the recommendations of The Aerosol Drug Management Improvement Team (ADMIT) [53–55] and in the most recent American advice [56].

How to choose a DPI?

The patient's preferences should be always discussed and considered when choosing an inhaler. The scheme of choosing the DPI by a physician, which has been proposed since several years by the experts, is shown in the Figure 4.

Summary

Dry powder inhalers have dominated the inhalation drugs market in many countries since several years. It is due to the numerous advantages of DPI and to the development of new, usually improved devices. A great diversity of DPI cause problems with selecting and using the inhalers by patients with asthma and COPD. The mistakes made during the utilisation of DPI result in many clinical consequences and cause important economic effects. The choice of an optimal DPI for a particular patient equally depends on competences of the physician and on preferences and competences of the patient. These elements finally define the correctness of the patient's inhalation technique and his compliance. They also determine the efficacy, safety and the patient's satisfaction from the recommended inhalation therapy.

Conflict of interest

The authors declare no conflict of interest.

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