

## TITLE PAGE

TITLE : COMMON ERRORS IN INHALATION THERAPY: IMPACT AND SOLUTIONS

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#### ABSTRACT

**OBJECTIVE:** Inhalation therapy is one of the key pillars in the treatment of chronic obstructive diseases, such as asthma and COPD( Chronic obstructive pulmonary disease) ; however, wide number of errors occur with high frequency in the inhalation manoeuvres among these patient. This review discuss the main errors made with inhalation devices, factors associated with poor IT( inhalation technique) , their consequences, and possible solutions.

**DATA SOURCES:** To do this, we performed a search of any publications available in PubMed between the years 2000 and 2019, using the key words: asthma, COPD, obstructive lung disease, inhalers, misuse, errors.

**STUDY SELECTIONS :** After a review of the titles and abstracts by the working group, the articles chosen were considered the most relevant in providing evidence of the problems and establishing solutions in the inhalation treatment of asthma and COPD.

RESULTS: There are several publications that associated the errors in the inhalation technique with a poor prognosis both of asthma and COPD. Most authors generally agree in that a poor IT is associated with poor control of the symptoms.

**CONCLUSIONS :**It is essential to review the IT in all our patients with asthma and COPD due to the high socio-economic impact that it involves; an effort must be made to homogenise the evaluation of IT, so that it helps to transmit a clear message to the patients, as well as to the health professionals on what is and what is not a correct manoeuvre.

## **COMMON ERRORS IN INHALATION THERAPY: A REAL PROBLEM**

### **INTRODUCTION**

Inhalation therapy is one of the key pillars in the treatment of chronic obstructive diseases, such as asthma and COPD (chronic obstructive pulmonary disease) (1,2,3). Hundreds of years ago Maimonides already defended the need for personalized patient management (4), which seems especially necessary with this type of treatment given the wide availability of devices and drug combinations, which are progressively increasing over the last years (5,6).



However, wide number of errors occur with high frequency in the inhalation manoeuvres among these patients (7), and this incorrect use is associated with poor control of the symptoms, an increase in exacerbations, as well as an increase in the use of social and health resources (8,9,10,11)

These errors in the use of inhalers add to the obvious problem of the low adherence to inhaled therapy by the patients, further limiting the likelihood of obtaining an effective response to these drugs (12) There has been a great variability in the frequency of incorrect technique detected, depending on the population, sometimes reaching 94% of the patients included, regardless of the device evaluated (8).

To check the inhalation technique of our patients is an obligatory step in our daily clinical practice, but it is not always easy to determine what is a good technique due to the lack of a clear consensus.

The aim of this article is to review the main errors made with inhalation devices, factors associated with poor IT ( inhalation technique), their consequences, and possible solutions.

## **METHODOLOGY**

To do this, we performed a search of any publications available in PubMed between the years 2000 and 2019, using the key words: asthma, COPD, obstructive lung disease, inhalers, misuse, errors. After a review of the titles and abstracts by the working group, the articles chosen were considered the most relevant in providing evidence of the problems and establishing solutions in the inhalation treatment of asthma and COPD.

## **CONCEPT OF A CORRECT INHALATION TECHNIQUE**

The steps required for a correct IT may involve the loading of the device (for example, to perforate the capsule, or correct opening of the device), the exhalation and the inhalation manoeuvre itself (such as the speed of inhalation) (10,13,14,15).

Different authors have set out criteria to define a correct IT, although significant differences are observed between them (16,17,18). This variability may partly explain the differences between the different studies on the prevalence of errors in IT.

In a systematic review of 38 studies published by Mahon et al, in 2017, as regards errors in IT in asthma and COPD, it was not possible to reach a definitive conclusion on a checklist on correct IT (18)

H. Chrystyn et al. in 2017 (10), mentions this problem; the lack of evidence in the evaluation of errors of the devices and the lack of standardised checklists.

Even with these difficulties, there is some agreement in some aspects of IT, and most publications include the following steps in order to be considered a correct IT (17,19-23):

Pressurised metered dose inhalers (pMDIs):

1. Preparation: remove the cap, shake, and hold the inhaler in a vertical position with the mouthpiece horizontal.
2. Exhale completely
3. Place the teeth and lips around the mouthpiece with the tongue below it and press or click the device whilst starting a slow inhalation.
4. Inhale slowly and deeply, without stopping
5. Hold the breath for 5 to 10 seconds or for as long as possible.
6. Put on the cap

Pressurised metered dose inhalers (pMDIs) with inhalation (holding) chamber:

1. Preparation: remove the cap, shake the inhaler whilst keeping it vertical.
2. Assemble the mouthpiece of the pMDi by the rear part of the inhalation chamber.
3. Exhale completely (down to residual volume)
4. Place the mouthpiece of the chamber between the teeth and close the lips around it.
5. Press the device once whilst inhaling slowly and deeply. Afterwards, hold the breath for between 5 to 10 seconds or the maximum possible.
6. Failing that, several slow and deep breaths can be made (at least 5) to the residual volume through an inhalation chamber.
7. Remove the pMDI from the chamber and put the cap on.

Dry powder inhalers (DPI):

1. Preparation: remove the cap, charge the device according to the manufacturer's instructions.
2. Exhale completely

3. Place the teeth and lips around the mouthpiece, sealing it.
4. Take a deep, fast, vigorous breath.
5. Hold the breath for 5 to 10 seconds or for as long as possible.
6. Put on the cap

There is also no unanimous consensus to define critical errors. Some of these steps are considered as critical errors by some authors, but not by others (14,15,16,17,19,20), as is the case of placing the device in the mouth and sealing with the lips (24), or removing the cap in the conventional pressurised devices (14,25)

The definition currently more accepted as a critical error (basic or crucial) is " that impedes the drug reaching the airways ,so that can affect the effectiveness of the administered drug and, thus, leads to a sub-optimal control of the asthma disease and COPD", whilst a non-critical error is that which is not classified as critical (21,22).

The significant heterogeneity between the studies makes it difficult to conclude which are most common errors in inhalation devices. The CRITIKAL study was the first study to observe associations between specific inhaler errors independently and after a multivariable analysis ( 22)

In a review published in 2013, Sanchís et al described the frequency of errors in each step of the different devices, pMDI, as well as DPI. The studies included were not homogeneous in their design, compromising the comparisons between different studies (26).

## **CAUSES OF A POOR INHALATION TECHNIQUE**

The causes of a poor IT are basically related to the type of device and with the characteristics of the patients.

### **RELATED TO THE TYPE OF DEVICE**

The search for the "ideal inhaler" in the last few years has meant that the current inhaler landscape is made up of:

- conventional pMDI devices,
- Modulite® devices,

- Respimat® system, an intermediate device between a conventional pressured one and a nebuliser,
- BAI (breath actuated inhaler), a pressurised device activated by the breathing of the patient, and
- 12 dry powder devices: 4 single-dose (Handihaler, Zonda, Aerolizer, Breezhaler), and 8 multi-dose (Turbuhaler, Accuhaler, Easyhaler, Novolizer, Genuair, Nexthaler, Ellipta, Spiromax).

This could be considered as an advantage due to the diversity of inhalation devices, and at the same time could become a handicap due to the added difficulty for the correct knowledge of the functioning of each one of them for the patients, and even for the medical prescribers themselves, particularly in Primary Care.

Among the characteristics that differentiate the devices are:

- type of formulation: suspensions or solutions.
- type of dispense: dry powder, pressurised, fine mist.
- single-dose or multi-dose
- disposable cartridges or with a reservoir
- system for device loading
- system for aerosolization: gas or spring pressure or patient's effort

Due to this diversity of devices, the chosen inhaler should be the most suited one to the characteristics, preferences and needs of the patient.

In the case of the pMDI devices, a slow and smooth inspiration flow is necessary, and in the case of the DPI devices, a greater inspiratory effort is required that will enable the powder particles to disaggregate in order to reach the distal airways as finer particles. (27)

For this reason, more patients confuse the inhalation technique when different devices are prescribed, and in many cases the required inspiratory flow is insufficient (10).

One of the support tools that we have available for choosing between one and another device according to the inspiratory flow of the patients is the In-Check DIAL G16 (28). It is a

maximum inspiratory flow meter with origins that go back to the 1960's, and is based on an adaptation of the original expiratory flow meter by Wright (29).

In 1990 Clement Clarke improved the initial device, creating the In- Check DIAL, and in the last few years, due to the appearance of new devices, it has evolved to the current In-Check DIAL G16, with the possibility of evaluating up to 15 different DPIs and conventional PMDis (30,31).

The Check DIAL bases the measuring of the different intrinsic resistances of the devices on turbulent flow through them following the formula  $\sqrt{P} = Q \times R$  (P: pressure gradient in the device; Q: inhalation flow; R: resistance of the device).

It can measure the inspiratory flow (in a range of 15-120 L/min, +/-10L/min) required for the activation of the different devices. This energy is what will generate the turbulence required in order that the powder is dispersed, and the different preparations are disaggregated (28,32).

## **ARE THERE PREDICTIVE FACTORS FOR ERRORS IN THE INHALATION TECHNIQUE RELATED TO THE CHARACTERISTICS OF THE PATIENT?**

It is considered that the different patient characteristics, such as age, gender, education level, number of inhalers prescribed, or having received prior instructions on the use of each inhaler, have an influence on the inhalation technique of our patients.

These are the factors most frequently studied, but the results in the literature are not conclusive:

1. Age: In a systematic review published by Usmani et al, including 114 articles, the relationship between age and IT was analysed in 29 of them. In 34% of the publications, a worse IT was observed with a higher age (11, 33-41).
2. Gender, in this same review, it was not possible to establish any significant difference in the IT as regards gender.
3. Education level: 20 of the 114 articles studied the relationship between education level and errors in the IT (11,42-56), observing a significantly more deficient IT in individuals with a low educational level in 45% of these publications (11,36,37,41,42,44,45,49,55).

#### 4. Number of devices prescribed:

Only 3 studies were found with data on the relationship between the number of devices used simultaneously by a patient and errors in IT.

In the study published by Batterink et al, in 2012 on a cohort of 37 patients with COPD, the mean (and standard deviation (SD)) prescription of different devices in this group was  $1.8 \pm 0.7$ . The patients with critical errors in the IT were using a mean of 2.1 different inhalers versus 1.5 in those that did not show critical errors (13). Similarly, Rootmensen et al, in a randomised clinical trial of 156 patients with asthma and COPD, 28% of these patients used different inhalation devices. The results of this study showed that there were two factors associated with a poor IT; not having received any previous education on IT, and the use of more than one inhalation device (OR: 2.2) (34).

Khassawneh et al, in 2008, pushed a multicentre observational study on a cohort of 300 patients with asthma and COPD. Incorrect handling was observed in 53.2% of the patients that were using only one device against 75.5% of those that were using more than one device ( $P=.001$ ). The independent predictive factors for an incorrect IT were the diagnosis of COPD compared to the diagnosis of asthma (adjusted OR: 3.45, 95% CI: 1.58-7.53); and using multiple inhalers compared to using a single device (OR: 2.92; 95% CI: 1.73-4.30) (57).

6. Prior instructions on the use of inhalers: of the 144 articles reviewed, 17 investigated the relationship between having received previous information on the use of the different devices and performing a correct IT in adults. In 28% of the reviewed articles, a significant relationship was observed between having received some previous education on the use of the devices and a better inhalation technique (11,39,58-65).

7. Other factors, such as having two or more comorbidities (45), obesity (44), heart disease (55), cognitive impairment (58), and a low socio-economic level (45) were evaluated in some studies, showing a significant relationship with a higher frequency of IT errors.

#### **MEASURES TO IMPROVE INHALATION TECHNIQUE**

Price et al, in an article published in 2013, described possible solutions regarding the poor use of inhalation devices. (16)

First, they proposed the need to investigate the lack of education and knowledge of our patients, and to demonstrate the improvement in clinical and economic parameters associated with a correct IT. The need for a greater involvement in the social-health policies is highlighted.

Finally clear, precise, and simple education that could be easily understood and remembered by patients is indispensable.

As regards this last point, and to highlight the usefulness of minimal intervention (as in other respiratory diseases, like smoking), in 2018 Schuermans et al, published a clinical trial with 160 patients, which demonstrated that a minimal educational intervention of 10 minutes in the intervention group significantly improved the proportion of patients with good asthma control after three months [Asthma Control Test (ACT) >19; 43% versus 77%,  $P<.001$ ], as well as improving knowledge on asthma treatment, the devices, and inhalation technique ( $P<.001$ ) (66).

Other authors propose other ways of educating by using audio-visual means in order to improve the learning in patients. Thus, Hye Yung Park published a randomised clinical trial in which the usefulness of education using visual means compared to the classic face to face education was demonstrated. The FEV1 improved significantly in the intervention group at 12 weeks after visual education in the sub-group of elderly patients. This study did not manage to demonstrate significant improvements in other independent variables like ACT or IT score (67).

Another educational method proposed by Papi and Virchow in 2011 consisted of several steps:

- 1.To correctly choose the device in accordance with the characteristics of the patients.
2. A more intensive intervention, repeating the demonstration several times until an adequate IT is achieved
3. Maintenance of the techniques using videos or descriptive material, and reviewing the IT on each visit (68)

## **POOR INHALATION TECHNIQUE AND POOR DISEASE CONTROL**

There are several publications that associated the errors in the inhalation technique with a poor prognosis both of asthma and COPD (Table 1).

Most authors generally agree in that a poor IT is associated with poor control of the symptoms (11,25,27,35,43,45,64-66,68-75)

Some of these studies also highlight the importance of an educational intervention, even a short minimal intervention of 10 minutes (35,57,59,64,66,73)

The CRITIKAL study is one of the largest studies carried out in real life and the results are consistent with evidence in the literature; the association between specific inhaler errors and poorer asthma control. It also demonstrates that errors are very frequent and device-specific(22).

## **POOR INHALATION TECHNIQUE AND INCREASE IN HEALTH COSTS**

The poor use of inhalers is associated with a higher number of hospital admissions, visits to A&E departments, a greater number of antibiotic courses, and oral steroids, leading to an increase in health costs.

In a study carried out on patients in real life (usual clinical practice) by Roggeri et al, in 2016, two cohorts of 100 patients with COPD were compared, one with at least one critical error in the inhalation technique against opposed to another cohort of 100 patients with no errors in the use of the inhalers. At the end of one year 11.5 more hospital admissions were observed, as well as 13 visits to A&E departments, 19.5 antibiotic courses, and 47 corticosteroid courses for the first cohort. On comparing the health costs, there was a annual 23,444 Euros/years overcost in the 100 patients of the cohort with a poor IT. The results were similar in a cohort of patients with asthma: in those patients with at least one critical error, increases in the hospital admissions rates (19) were observed, as well as visits to A&E departments (26.5), antibiotic courses (4.5), and oral corticosteroid cycles (21.5), compared to the cohort with a good IT. As a result, in the patient cohort with asthma and a poor IT, an increase in



health costs of 44,104 Euros/year was observed in the 100 patients with asthma included in the study (9)

## **HAS THE INHALATION TECHNIQUE IMPROVED OVER TIME?**

Data on IT evolution is not favourable, with an elevated error frequency being maintained in the long term. Sanchis et al analysed the evolution of IT over a period of 40 years, including studies published between the years 1975 and 2015. After the analysis of 144 articles, it was observed that the rates of incorrect inhalation technique remained stable during the period analysed (76).

## **CONCLUSIONS**

Given the elevated prevalence of incorrect IT, its negative impact on the results of the diseases treated, and the failure that entails the virtually zero improvement of the IT over the last 40 years, it seems necessary to look for solutions to improve this situation.

It is essential to review the IT in all our patients with asthma and COPD due to the high socio-economic impact that it involves.

Firstly, an attempt should be made to reduce the prescribing of different devices, trying to use the same type of device, whenever possible, given the association between a higher number of devices and an incorrect IT.

Secondly, the choice of the device must be adapted to the type and preferences of the patient. There are differences in the operation of the inhalers that can make some of them difficult to use depending on the abilities of the patient, such as the inspiratory capacity, manual dexterity, or visual acuity.

Thirdly, it seems clear that educational measures have a positive impact on different aspects of these diseases, including IT (77).

Finally, an effort must be made to homogenise the evaluation of IT, so that it helps to transmit a clear message to the patients, as well as to the health professionals on what is and what is not a correct manoeuvre.

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TABLE 1. PRINCIPAL INTERVENTIONAL AND NON -INTERVENTIONAL STUDIES IN INHALATION TECHNIQUE .

	Study design							
Al -Jadhali, 2013(25)	Cross-sectional, two-centre	ND	450	Asthma	>18y	Pmdi,PMDI+S,TH, Diskus	Age, gender, level of studies, ACT, devices, previous asthma education A&E visits, poor inhalation technique Asthma duration	Poor inhalation technique is associated with ACT<15 (P=.001 ), three or more A&E visits ( P=.0497) and irregular follow-up(P=.0001)
Baddar, 2014(69)	Cross-sectional, two-centre	ND	218	Asthma	12-72y	ND	Age, gender, ACT, check-list errors, adherence,	Poor inhalation technique is associated

							rhinitis, maintenance tto.	with poor control (OR: 5.3; 95% CI: 2.05-14). Poor adherence is associated with poor control (OR :7,4; 95% CI : 3.5-15.8)
Bathwal, 2009(59)	Non-randomised prospective single- centre trial	Educational program	172	Asthma	>12y	Pmdi,PMDI+S,DPI	Age, gender, Asthma control (GINA),poor IT previous asthma education, no scheduled visits	Better disease control after asthma education program ( P>.05
Basheti, 2008(60)	Simple, blind, randomised trial	Educational program	97	Asthma	>14y	Th, Diskus	Peak-flow variability, Asthma	After education program,

							severity /Australian Asthma Management Handbook	improvement of the inhalation technique in active group ( P<.001) and in the asthma severity ( P=.0015)
Coelho,2011(43)	Cross-sectional single-centre		467	Asthma	>18y	Pmdi, PMDI+s, Pulvinal, Aerolizer	Age, gender, level of studies, check- list errors, devices, ACQ6, asthma duration, use of tto >3 months	A good inhalation technique with Aerolizer is associated with good asthma control (P=.04)
Dalcin, 2014(45)	Cross-sectional single-centre		268	Asthma	>14 y	Pmdi, DPI	Age, gender, race, marital status, Level of studies, Family	Poor inhalation technique is associated

							income, Tobacco, number of comorbidities, Asthma severity (GINA), Asthma control (GINA), functional values.	with poor control of the disease (P=.002)
Fernandes, 2011(70)	Trial, randomised, controlled	Educational program	89	Asthma	ND		Age, gender, ACT	Significant improvement in control of asthma in the intervention group (P<.05)
García- Cardenas, 2013(71)	Multicentre randomised controlled trial	Educational program	336	Asthma	>18y	TH	Age, gender, BMI, tobacco, marital status, Level of studies,	ACQ improved in the intervention group (P<.001) and an

							marital status, occupational status, ACQ, check-list errors, adherence, asthma tto controller	increase of 30.1% of patients with good control (P<.001)
Giraud,2011(27)	Observational, prospective Multicentre,		727	Asthma		Pmdi, autohaler, easybreathe Autohaler,	Age, gender, tobacco, type of device, adherence, ACQ, check-list errors, previous education	ACQ improved from 1.8 to 1.4 (P<.001) after education session
Giraud, 2011(35)	Observational, prospective Multicentre,		6512	Asthma	>18y		Age, gender, BMI, tobacco, asthma duration, ACQ, previous cycles of GCO and	Factors associated with poor IT are advanced age (>50), tobacco, and

							antibiotics, check-list errors, asthma tto controller	poor asthma control (P<.001)
Góris, 2013(61)	Experimental (clinical trial)  Single-centre	Educational program	69	COPD	ND	Pmdi, TH, Aerolizer, Handihaler, Diskus	Age, gender, BORG, MRC, SGRQ, check- list errors, Level of studies, severity of COPD, disease duration, spirometry.	Number of exacerbations, attendances in A&E and hospital admissions were greater in the control group
Kuna, 2015(63)	Trial, prospective, observational, non- interventional, multicentre	Educational program	16844	Asthma	<16->76y	Pmdi	Age, gender, tobacco, BMI, physical activity, level of studies, asthma duration, Asthma	Improvement in asthma control in V2 is associated with an adequate inhalation technique (OR;

							control (GINA), number of exacerbations, SABA use, BUD/F dose, Asthma family background, exacerbations reason	1.48; 95% CI; 1.25-1.74; P<.001) and in V3 (OR; 1.66; 95% CI; 1.26-2.18; P<.001)
Levy, 2013(72)	Observational, prospective, Multicentre,			Asthma	>12y	Pmdi, PMDI+S, DPI, autohaler, easybreathe	Age, type of devices GINA control, previous cycles of GCO, check-list errors, asthma maintenance tto.	Poor IT is observed 4 times more in patients with poor symptoms control and two times more in patients with partial control (P<.0001, X2 value 281.19).



								The number of exacerbations was higher in the patients that had an incorrect IT (68%, P=.3)
Maricoto, 2015(73)	Cross-sectional, single-centre		62	Asthma / COPD >18y		Pmdi, PMDI+S, DPI	Age, gender, ACT, CARAT, Mmrc, CAT, spirometry, satO2, check-list errors, years diagnosed, previous IT education.	Relationship between number of errors and ACT (P=.032) and CARAT (P=.008) in asthma. No significant association was found between quality of IT and disease in the COPD

								group.
Melani, 2011(11)	Cross-sectional, Multicentre		1664	Asthma/ COPD		pMDI DPI (aerolizer, Diskus Handihaler, TH)	Age, gender, tobacco, spirometry, ACT, Mmrc, A&E, hospital admissions, device type, asthma maintenance tto., satO2, cycles of GCO and antibiotics previous year	Poor IT is associated with an increase in the risk of hospital admissions (P=.001), A&E attendances (P<.001) cycles of GCO (P<.001) and antibiotics P<.001), worse control of disease (.0001)
Plaza, 2015(64)	Clinical trial, randomised, controlled, Multicentre	Educational program	230	Asthma	18-70y	ND	Age, gender, BMI, ACT, tobacco, Level of studies, Charlson, mini	Significant improvement in the intervention group and gold

							AQLQ, functional values, cycles of GCO and antibiotics, A&E visits. hospital admissions, maintenance tto.	standard group of ACT (P<.001), exacerbations (P=.003) and mini AQLQ(P=.019)
Sulaiman, 2016(74)	Clinical trial, prospective, randomised, simple blind, Multicentre	Intensive educational program	221	Asthma	>18y	Diskus	Age, gender, tobacco, ACT, AQLQ	Intensive education in IT improved adherence (P=.02) and increased the percentage of patients with good asthma control
Yildiz, 2014(75)	Study, observational		572	Asthma	>18y	Pmdi, Diskus TH, Aerolizer	Age, gender, years of	Improved asthma control

							disease, tobacco, level of studies, work activity, ACT, check-list errors.	with an improved IT, and a decrease in the number of basic errors
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Pmdi: Pressurized metered dose inhaler;PMDI+S: pressurized metered dose inhaler spacer;TH : turbuhaler;ND : nor determinant; DPI : dry power inhalers; A&E:Aid and Emergencies ; IT: inhalation technique; BMI: body mass index; ACT: asthma control test; ACQ: asma control questionnaire; GCO: oral glucocorticoids;MRC: Medical Research Council; SGRQ:St. George's Respiratory Questionnaire; COPD: Chronic Obstructive Pulmonary Disease;SABA: short acting beta agonists; BUD/F : budesonide/formoterol; CARAT : Control of Allergic Rhinitis and Asthma Test;Mmrc: modified Medical Research Council; CAT : COPD Assessment Test;AQLQ: Asthma Quality of Life Questionnaire