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# Inhaler mishandling remains common in real life and is associated with reduced disease control

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**Summary**
Proper inhaler technique is crucial for effective management of asthma and COPD. This multicentre, cross-sectional, observational study investigates the prevalence of inhaler mishandling in a large population of experienced patients referring to chest clinics; to analyze the variables associated with misuse and the relationship between inhaler handling and health-care resources use and disease control.

We enrolled 1664 adult subjects (mean age 62 years) affected mostly by COPD (52%) and asthma (42%). Respectively, 843 and 1113 patients were using MDIs and DPIs at home; of the latter, the users of Aerolizer®, Diskus®, HandiHaler® and Turbuhaler® were 82, 467, 505 and 361.

*Abbreviations:* COPD, chronic obstructive pulmonary disease; MDI, press-and-breathe metered dose inhaler; DPI, dry powder inhaler; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; ACT, asthma control test; ICS, inhaled corticosteroids; LABA, long-acting beta-2-agonists; SABA, short-acting beta-2-agonists; MRC, medical research council; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity.

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We have a total of 2288 records of inhaler technique. Critical mistakes were widely distributed among users of all the inhalers, ranging from 12% for MDIs, 35% for Diskus® and HandiHaler® and 44% for Turbuhaler®. Independently of the inhaler, we found the strongest association between inhaler misuse and older age ($p = 0.008$), lower schooling ($p = 0.001$) and lack of instruction received for inhaler technique by health caregivers ($p < 0.001$). Inhaler misuse was associated with increased risk of hospitalization ($p = 0.001$), emergency room visits ($p < 0.001$), courses of oral steroids ($p < 0.001$) and antimicrobials ($p < 0.001$) and poor disease control evaluated as an ACT score for the asthmatics ($p < 0.0001$) and the whole population ($p < 0.0001$).

We conclude that inhaler mishandling continues to be common in experienced outpatients referring to chest clinics and associated with increased unscheduled health-care resource use and poor clinical control. Instruction by health caregivers is the only modifiable factor useful for reducing inhaler mishandling


## Introduction

Asthma and Chronic Obstructive Pulmonary Disease (COPD) guidelines increasingly rely on pharmacological management with inhaled drugs. Press-and-breathe Metered Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs) are the most commonly used delivery devices for administering aerosolised drugs.

Effective use of inhalers requires proper inhalation technique. Chlorofluorocarbon (CFC)—MDIs were the first marketed inhalers; their misuse has been observed to be common shortly after their introduction into clinical practice[1] and associated with poor clinical outcomes, such as reduced bronchodilation[2] and decreased disease control[3] in asthmatics. Manufacturers introduced DPIs as user-friendly devices. Being breath-actuated, DPIs overcome the difficulties between inhaler actuation and inspiration, one the most common errors with MDIs. However, a recent review[4] has shown that misuse of DPIs is also common in real life. Whether DPIs mishandling can have clinical consequences seems to be logical, but it is not demonstrated.[4] Although poor inhaler use is more common in older ages,[5] its impact on outcomes of COPD patients is also unknown, as most real-life studies on inhalation technique have been carried out on asthmatics.[6]

The aim of the present study was to evaluate the inhalation technique of a large sample of experienced outpatients referring to chest clinics; to investigate the prevalence and the factors associated with inhaler misuse; to assess the relationship between inhalation technique and some clinical outcomes.

## Materials and methods

The GENEBI (AIPO Gruppo Educazionale for NEBulizers and Inhalers) Project is a cross-sectional, observational study (ClinicalTrials.gov. identifier: NCT0925-0586) carried out in 24 chest clinics (see centers listed in appendix) throughout Italy. The centers were located at different latitudes across Italy and included highly urbanized as well as rural areas, encompassing a wide range of settings. The study was performed from July to September 2008.

During the study period all adolescent and adult (age greater than 14 years) outpatients, attending one of the participating centers for a scheduled visit and using an inhaler regularly at home were considered eligible for participation. Regular use was defined as utilization of an inhaler therapy at least once daily for 4 weeks in the 3 months before the enrollment. To meet the busy clinical practice with limited time, but to minimize selection bias, investigators were required to enroll their first two consecutive eligible patients in each working day. The enrollment always occurred after full explanation of the study and written informed consent; no one refused to participate to the survey. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the ethics committee of the participating centers.

Firstly, enrolled patients completed a standardized questionnaire prepared by the Educational Group members of the Italian Association of Hospital Pulmonologists (see translation from the original Italian format in supplementary data file). The comprehensibility and the reliability of the items had been previously tested by a group of patients not enrolled in the present study, previously described in detail.[5] Briefly, each questionnaire consisted of a general section and specific parts, each related to a specific inhaler. For practical and statistical reasons, we restricted our evaluation to MDIs, Aerolizer®, Diskus®, HandiHaler®, and Turbuhaler®, which at present are the most commonly used inhalers in Italy. Both the general and the specific sections included a self-compiled and an investigator-filled part. The self-compiled general section included some closed-type questions, which, after gathering some demographic information, investigated clinical data mostly related to the respiratory disease control in the last period. Because we had estimated that asthma was one of the most commonly encountered respiratory diseases, we have included the Asthma Control Test (ACT),[7] extending it to all enrolled patients. We have also used the modified Medical Research Council dyspnoea scale,[8] a validated tool which relates to measurements of health status in COPD patients. Respondents were also asked for unscheduled medical interventions due to their respiratory disease, such as visits to an emergency room, and/or hospital admissions, and/or antimicrobial treatments, and/or courses of corticosteroid tablets in the last year; being these data retrospectively collected, the degree of utilized

health-care resources could not be influenced by the investigators. Each specific self-compiled part included queries about the use of inhaled treatment, the source and the modalities of education to inhalation technique received. The physician-filled part evaluated the primary respiratory diagnosis, the baseline oxyhaemoglobin saturation whilst breathing air at rest, the prescribed inhaler devices and the drugs used. On enrollment, subjects underwent spirometry, performed and reported according to accepted guidelines.[9]

Then, each patient demonstrated the inhalation technique with all used devices to the investigator in a quiet area using a placebo device. Patients were asked to use their aerosol just as if they would be at home. For each center, a single trained investigator evaluated the modalities of inhaler use; to standardize their findings, periodic meetings were held with all the participating observers. Investigators were blinded to the results of the self-administered questionnaire when recording the mode of inhalation. All observations of inhaler use were reported in accordance to a standardized device checklist described into the questionnaire. Preliminarily, we had chosen to focus the analysis of results on critical errors (see their description in Tables 1 and 2), which are likely to make therapy with aerosols useless, according to previous literature.[10]

Statistical analysis was performed using generalized linear models (Stata 9, www.stata.com) with Gaussian or binomial/logit family, as appropriate, including the center as a cluster (which corresponds to adding it as a random effect variable) to obtain a robust standard error. Unless stated otherwise, age, level of education and respiratory diagnosis (COPD, asthma or other) was included as fixed effect variables in all models. Data are presented as the mean $\pm$ Standard Error unless otherwise specified. A $p$-value of $<0.05$ for a two-tailed test was considered as significant.

## Results

We enrolled 1664 subjects. The most frequent respiratory diagnosis was COPD or asthma. Some demographic and clinical characteristics of studied patients are displayed in Table 3. As expected, there were significant differences in smoking status (smokers and ex-smokers vs. never-smokers), sex, age and spirometric parameters between groups with asthma and COPD ($p < 0.0001$).

One thousand-one-hundred-and-thirteen patients were using DPIs; 843 were using MDIs; of the latter, only 32 (4%) in association with a valved holding chamber. Respectively, 65% and 83% of Diskus® and HandiHaler® users suffered from COPD; subjects using Diskus® and HandiHaler® prevailed among COPD patients ($p < 0.0001$), while we did not find any difference for the other studied inhalers according to the respiratory diagnosis. Six-hundred-ten (37% of total) patients were using more than one type of different inhaler; most of these (82%) had a diagnosis of COPD. Of subjects using both Inhaled Corticosteroids (ICS) and Long-Acting Beta-2-Agonists (LABA), 92.5% had prescribed a combination inhaler and 7.5% separated inhalers.

We have recorded 2288 observations of inhalation technique for 1633 patients (data of 31 patients were lacking or missed). These findings occurred for a single, two and more than two devices, respectively in 1098, 506 and 48 cases. In Tables 1 and 2, we have reported the results of these observations. Mistakes were widely distributed among users of all the inhalers. According to our arbitrary criteria, at least one critical error for MDI, Diskus®, HandiHaler® and Turbuhaler® was respectively observed for 12%, 34.5%, 35% and 43.5% of users. A logistic analysis showed that patients using the Diskus® (OR $3.4 \pm 0.9$; $p = 0.0001$), the HandiHaler® ($3.1 \pm 0.8$; $p = 0.0001$) and the Turbuhaler® ($6.0 \pm 1.8$; $p < 0.0001$) had an increased risk of committing critical errors compared to MDIs users; patients using the Diskus® (Odds Ratio $0.6 \pm 0.1$;

**Table 1** Step-by-step MDI checklist of proper inhalation technique and errors recorded in our population.[a]

| Correct step of inhalation technique | Checklist of inhalation technique errors | Errors, % of users |
|---|---|---|
| Remove mouthpiece cap | Failure to remove cap* | 0.15 |
| Shake inhaler (suspensions only) | Not shaking the inhaler | 37 |
| Breathe out before firing | No exhalation before actuation | 50 |
| Inhaler upright during firing | Not holding the inhaler in the upright position | 9 |
| One inhalation for actuation | More actuations for a single inhalation | 19 |
| Place mouthpiece between lips and over tongue | Actuation against teeth, lips, or tongue*,[b] | 0.7 |
| Actuation in the first half of inhalation | Actuation in the second half of inspiration | 18 |
| | Activation after end of inhalation* | 5 |
| Fire while breathing in deeply and slowly and continue until total lung capacity | Stopping inhalation immediately after firing* | 10 |
| | Forceful inhalation | 52 |
| Inhalation by mouth | Inhalation through nose whilst and after actuation* | 2 |
| Hold breath for 10 s | No or short (less than 2–3 s) breath-holding after inhalation | 53 |

* = critical errors.

[a] All data are presented as the percentage of patients performing the uncorrected step compared to the total number of observations.

[b] Hold the mouthpiece inhaler between open lips (19% of total) or even a few centimeters from the open mouth is an acceptable alternative to place the mouthpiece between closed lips.

**Table 2** Step-by-step DPI checklist of proper inhalation technique and errors recorded in our population.[a]

| Correct step of inhalation technique | Checklist of inhalation technique errors | Errors, % of HandiHaler/ Aerolizer[a] users | Errors, % of Diskus users | Errors, % of Turbuhaler users |
|---|---|---|---|---|
| | Failure of priming* | | | |
| Remove or turn cover | Failure to open the device | 0 | 0.65 | 0 |
| Correctly insert capsule | Failure to insert the capsule | 9 | NA | NA |
| Pierce capsule | Failure to pierce the capsule | 3 | NA | NA |
| | Failure of loading* | | | |
| Load dose | Incorrect dose loading | NA | 7.3 | 14 |
| Hold inhaler upright | Keep the inhaler inclined no more than 45 from the vertical axis during loading | NA | NA | 23 |
| Breathe out the device mouthpiece | Exhaling into the device mouthpiece after loading | 19 | 22 | 14 |
| Inhale deeply and quickly | Stopping inhaling prematurely (not inhaling to TLC) | 26 | 29 | 22 |
| Inhale by mouth | Inhaling by nose* | 2 | 1 | 0 |
| Place mouthpiece between lips | Not sealing lips around mouthpiece during inhalation* | 5 | 5 | 4 |
| Forceful and deep inhalation | Slow and not forceful inhalation* | 24 | 28 | 22 |
| Breathe out the device mouthpiece | Exhaling into the device mouthpiece after inhalation | 19 | 21 | 11 |
| Breath-hold | No breath-holding after inhalation | 25 | 32 | 28 |
| Control if capsule is broken and does not contain residual powder | Do not control whether some powder drug rests into the capsule after inhalation | 30 | N.A. | N.A. |

All data are presented as the percentage of subjects performing the uncorrected step compared to the total number of observations; *: Critical errors; N.A.: not applicable to the device.
[a] Due to the similar instructions of use, the records of HandiHaler® and Aerolizer® have been grouped in a single column.

**Table 3** Some demographic and clinical characteristics of enrolled patients even according to the primary respiratory diagnosis.

| Characteristic | COPD ($n$ = 864) | Asthma ($n$ = 703) | Other ($n$ = 97) | Total($n$ = 1664) |
|---|---|---|---|---|
| Male, % of total[a] | 78 | 43 | 54 | 58 |
| Age, mean ± SD, years[a] | 70 ± 10 | 51 ± 17 | 63 ± 16 | 62 ± 16 |
| Smoking status, %[a] | | | | |
| Smokers | 18 | 11 | 16 | 15 |
| Ex-smokers | 71 | 31 | 45 | 51 |
| Never smokers | 11 | 58 | 39 | 34 |
| Mean $FEV_1$% pred ± SD[b] | 60 ± 20 | 80 ± 23 | 77 ± 20 | 69 ± 24 |
| Mean $FEV_1$/VC ± SD, %[b] | 60 ± 14 | 72 ± 15 | 76 ± 12 | 66 ± 16 |
| Diskus users[b] | 302 | 141 | 24 | 467 |
| HandiHaler users[b] | 421 | 58 | 26 | 505 |
| MDIs users[b] | 356 | 443 | 44 | 843 |
| Aerolizer users[b] | 42 | 35 | 5 | 82 |
| Turbohaler users[b] | 159 | 178 | 24 | 361 |
| LABA (not ICS) users[b] | 18 | 22 | 7 | 47 |
| ICS (no LABA) users[b] | 18 | 82 | 8 | 108 |
| ICS/LABA users[b] | 759 | 455 | 60 | 1274 |
| SABA users[b] | 52 | 49 | 7 | 108 |
| Sputum >3 months per year in the 2 last years[a] | 460 | 202 | 33 | 695 |

[a] According to the self-compiled part of the questionnaire.
[b] According to the investigator-filled part of the questionnaire. MDI = Press-and-breathe Metered Dose Inhaler; PN = Predicted normal ICS = Inhaled Corticosteroids; LABA = Long-Acting Beta-2-Agonists; SABA = Short-Acting Beta-2-Agonists; COPD = Chronic Obstructive Pulmonary disease; $FEV_1$ = Forced Expiratory Volume in 1 s; FVC = Forced Vital Capacity.

**Table 4** Percentage of observations with at least one critical inhaler error for the whole population and the groups with asthma and COPD according to the items of the ACT.[a]

| Answer | COPD % | Asthma % | Total % | OR ± SE; P level[b,c] |
|---|---|---|---|---|
| Limited doing desired everyday life for respiratory symptoms | | | | |
| All the time | 36 | 14 | 32 | 1.58 ± 0.06; $p = 0.00001$ |
| Often | 34 | 30 | 33 | |
| Sometimes | 33 | 33 | 31 | |
| Seldom | 25 | 25 | 22 | |
| Not at all | 27 | 27 | 21 | |
| Frequency of shortness of breath | | | | |
| More than once a day | 30 | 28 | 30 | 1.32 ± 0.13; $p = 0.03$ |
| Once a day | 35 | 15 | 29 | |
| A few (3—6) times a week | 38 | 24 | 34 | |
| Once or twice a week | 30 | 23 | 27 | |
| Not at all | 23 | 18 | 21 | |
| Use of rescue inhaler | | | | |
| 3 or more times a day | 33 | 26 | 28 | 1.28 ± 0.13; $p = 0.02$ |
| 1 or 2 times per day | 35 | 26 | 33 | |
| A few times a week | 22 | 22 | 22 | |
| Once a week or less | 27 | 18 | 22 | |
| Not al all | 33 | 33 | 28 | |
| Rate respiratory disease control | | | | |
| Not at all | 34 | 22 | 29 | 1.56 ± 0.15; $p < 0.00001$ |
| Poorly controlled | 30 | 27 | 29 | |
| Somewhat controlled | 37 | 32 | 36 | |
| Well controlled | 30 | 21 | 27 | |
| Fully controlled | 26 | 16 | 21 | |
| Sleep disturbance for respiratory symptoms, % | | | | |
| Four or more nights a week | 39 | 21 | 29 | 1.29 ± 0.12; $p = 0.009$ |
| 2 or 3 nights a week | 30 | 24 | 28 | |
| Once a week | 35 | 25 | 32 | |
| Once or twice | 37 | 18 | 29 | |
| Not at all | 27 | 21 | 24 | |

[a] The ACT test requires that patients recall their experience over the past 30 days and respond to each question using a 5-points Likert scale where 1 reflects no impairment and 5 maximum impairment.
[b] Relationship between risk of at least one critical inhaler error and question score.
[c] Ordered logistic regression adjusted by diagnosis, type of inhaler and patients with more observations (due to use of more than one type of inhaler) and evaluated by $\chi^2$ for trend.

$p = 0.002$) and the HandiHaler® (OR 0.5 ± 0.1; $p = 0.0001$) performed better than the Turbuhaler® users.

Regarding the aim of predicting the factors associated with faulty inhaler technique, we organized a logistic model where, after adjusting for different device, the risk of critical errors increased with age (OR 1.12 ± 0.01; $p = 0.008$) and was reduced for higher degree of education (OR 0.77 ± 0.06; $p = 0.001$). Females showed a not significant trend for a reduced risk of inhaler misuse (OR 0.74 ± 0.12; $p = 0.064$). The rate of critical errors was not associated with the FEV1/VC ratio (OR 1.01 ± 0.01; $p = 0.23$) and the FEV1 (OR 1.00 ± 0.03; $p = 0.93$). After adjustment for age, patients using a single type of inhaler did not perform critical errors more often than those using two or more different devices (OR 0.89 ± 0.11; $p = 0.27$). Fifty-one-percent of COPD patients had a modified Medical Research Council dyspnoea scale score greater than 2; there was no association between COPD patients with critical inhaler errors and MRC score (OR 1.10 ± 0.07; $p = 0.75$). After adjustment for age, there was no relationship between risk of at least one critical inhaler error and the presence of chronic phlegm (OR 1.03 ± 0.11; $p = 0.45$). Asthmatics had a lower risk of critical errors than COPD patients (OR 0.59 ± 0.12; $p = 0.002$), but this relationship disappeared after adjustment for device, age and level of instruction (OR 1.1 ± 0.3; $p = 0.62$). Subjects with a resting oxyhaemoglobin saturation value greater than 90% did not differ in risk of inhaler misuse with respect to more hypoxemic ones (OR 1.01 ± 0.25; $p = 0.96$). There was an association between subjects who did report no or little perceived benefit from inhaler use and inhaler misuse (OR 1.4 ± 0.2; $p = 0.015$). The percentage of observations with at least one critical inhaler error for the whole population and the groups with asthma and COPD according to each item of the ACT are shown in Table 4; overall, there was an association between ACT score and risk of critical error (OR 1.53 ± 0.14; $p < 0.0001$) as a whole, but even considering separately the group of asthmatic (OR 1.73 ± 0.26;

**Table 5** Percentage of observations of inhaler technique (yes = at least a critical error; no = no inhaler error) for the groups of asthmatic and COPD subjects according to some unscheduled health-care resources use in the last year.

| Characteristic | COPD | | Asthma | | OR ± SE; P level[a,b] |
|---|---|---|---|---|---|
| At least a critical inhaler error | No | Yes | No | Yes | |
| Hospital admissions, % | | | | | |
| Never | 62 | 55 | 86 | 76 | 1.47 ± 0.17; $p = 0.001$ |
| 1 | 23 | 26 | 9 | 13 | |
| 2–3 | 11 | 16 | 3 | 9 | |
| >3 | 4 | 3 | 2 | 2 | |
| Emergency department visits, % | | | | | |
| Never | 71 | 64 | 81 | 69 | 1.62 ± 0.20; $p = 0.0006$ |
| 1 | 22 | 24 | 11 | 16 | |
| 2–3 | 4 | 10 | 3 | 10 | |
| >3 | 3 | 2 | 4 | 5 | |
| Antimicrobic courses, % | | | | | |
| Never | 30 | 20 | 41 | 34 | 1.50 ± 0.15; $p = 0.00004$ |
| 1 | 29 | 31 | 30 | 25 | |
| 2–3 | 26 | 33 | 18 | 17 | |
| >3 | 15 | 15 | 11 | 14 | |
| Corticosteroid courses, % | | | | | |
| Never | 37 | 29 | 35 | 27 | 1.54 ± 0.16; $p = 0.00003$ |
| 1 | 22 | 19 | 30 | 35 | |
| 2–3 | 30 | 26 | 22 | 19 | |
| >3 | 11 | 26 | 13 | 19 | |

[a] Relationship between risk of at least a critical inhaler error and self-report of some unscheduled health-care resources use in the last year.
[b] Ordered logistic regression adjusted by diagnosis and type of inhaler and evaluated by $\chi 2$ for trend.

$p < 0.0001$) and COPD patients (OR 1.46 ± 0.18; $p < 0.005$). In Table 5 we have described the percentages of observations with critical inhaler errors (yes = at least a critical error; no = no inhaler errors) for the groups of asthmatic and COPD subjects according to some unscheduled health-care resources use in the last year; the finding of critical errors in inhalation technique was also associated with increased risk of hospitalization ($p = 0.001$), emergency room visits ($p < 0.001$), use of antibiotics ($p < 0.001$) and courses of oral corticosteroids ($p < 0.001$); again, there was always a statistical significance ($p < 0.05$) even considering separately asthmatics and COPD patients. Regarding inhaler education by health caregivers, our population included one third of patients reporting no education (including 7% who had indicated reading the patient information leaflet with no further explanation), another third only with verbal instruction and the latter third (34% of total) of patients having received practical demonstration using a placebo inhaler. Given that our participants were enrolled in chest clinics, a respiratory specialist was by far the most common source of instruction for inhalation technique (58% of total); other sources of instruction were general practitioners (18%), nurse (15%) and pharmacists (3%). Patients who had received instruction by chest physicians were associated to a lower risk of critical inhalation errors for all the studied devices (OR 0.71 ± 0.11; $p < 0.03$). On the contrary, the lack of instruction by health caregivers increased the risk of critical errors (OR 2.28 ± 0.05; $p < 0.001$). A check-up of proper inhalation technique at follow-up visits was never organized for 276 (35% of total), once for 130 (24%) and more than once for 107 (20%) subjects. Thus, patients who had been checked (OR 0.70 ± 0.07; $p = 0.0001$) at least once for mastering good inhaler practice at follow-up visits had a lower risk of critical inhalation errors for all the studied devices.

## Discussion

Inhalation is the preferred route for administering drugs to asthma and COPD patients. Despite advancements in technology, which have permitted the introduction of more user-friendly devices, our study has shown that inhaler mishandling remains a serious issue for currently available inhalers. Previously, it had been suggested that it was easier to learn how to use a DPI as compared to a CFC-MDI.[6,11,12] Unfortunately, in real life, as our study has confirmed, many patients did not receive any inhaler education. No education by health caregivers on inhaler technique consistently increased the risk of misuse for all the studied devices. In another survey with a similar study design carried out on 2001–2002, approximately 80% of our patients reported some education of good inhaler technique by health caregivers (vs. 67% of the present survey) and two third (vs. 34% of the present survey) received a practical demonstration of use.[5] We think that the increasing current busy clinical practice and the introduction of newer devices marketed as user-friendly may possible favourite reduced rates of inhaler education in current real life.

We found that the rate of critical errors for DPIs was not lower than that of MDIs. This result has to be evaluated

cautiously, as our survey was not designed to compare different devices and our choice of critical errors was not balanced between inhalers. Likewise, it is difficult to organize a comparison between studies, because there is no agreement for any device regarding the clinically significant inhaler mishandlings. For example, no breath-holding and no full exhalation to residual volume have been reported as the most common errors using DPIs,[4] but they do not seem to reduce lung drug delivery.[13,14] No full exhalation has been described as an error for MDIs, but a comfortable exhalation just below or over functional respiratory capacity is a clinically acceptable alternative.[15] Advancements in device technology also contribute to modify the concept of inhalation error over time: failing to shake the MDI before actuation has no effect on drug delivery in case of solutions, while inadequate mixing of the canister content has been reported to reduce lung deposition up to 50% with suspensions.[16] Although our choice of critical errors is based on previous literature,[10] it is arbitrary and deserves discussion. Regarding the MDIs, the failure to remove cap and incorrect firing was occasionally observed. Inhalation through nose was reported in 2% of our subjects as well as in the literature.[15] It has been reported[15] that 27% of MDI users showed poor hand-lung coordination; however, this problem involves several levels and different clinical consequences: we considered as a critical error firing after inspiration was completed or during exhalation: 5% of our subjects showed this critical mistake, a value in accordance to a previous review[15] where 4% of MDI users actuated the canister at end of inspiration. Firing the canister in the second half of inhalation may reduce lung deposition using the CFC-MDIs,[17–20] but it is not critical using extra-fine newer MDIs.[21] We considered the cold-freon effect as another critical error that we observed in 10% of our patients, a percentage similar to the 6% previously reported.[15]

Effective use of DPI requires that each dose must be primed and loaded. We have observed similar rates of failure (8–11%) for this type of critical error with all the studied DPIs except for Turbuhaler® (29%), which has position-sensitive loading; this difficulty explains the increased level of mishandling in this phase using this device in our as well as other large studies.[22,23] DPIs derive the energy for the emptying of the drug system from the user inspiratory flow: the failure to achieve a forceful inspiratory flow through a device is the most common critical mishandling with DPIs in our series, amounting to 26–29% according to the different inhaler. Slow inhalation has been often described as an inhaler mishandling.[5,12,24] Lenney et al.[12] indicated slow inhalation as a reason for reduced (and not critical!) lung drug delivery. We are aware that our evaluation of slow inhalation through a certain DPI as critical error is subjective, but we think that this finding can be real and clinically relevant, because we have largely discussed this topic in previous meetings and decided to include as "slow" inhalation only well defined observations: for instance, for Aerolizer® and Handihaler®, when investigators did not hear the capsule vibrate, which occurred in 24% of our observations. In another observational study of ours, respectively, of two groups of 44 and 62 patients showing slow inhalation through the Turbuhaler® and the Diskus® by direct observation, 34 (77%) and 37 (60%) demonstrated a Peak Inspiratory Flow (PIF) lower than 30 l/min using the In-Check Dial®; interestingly, 102 of these 106 patients achieved a PIF of at least 30 l/min after proper education.[24] Likewise, our results mirrored those reported using objective methods in populations similar to ours.[25,26] Nsour et al.[25] observed a slow inhalation flow through the Turbuhaler® (<30 L/min) in 19% of 74 elderly COPD patients by using the In-Check Dial®. Kamin et al.,[26] assessing the inhalation quality by the Inhalation Manager® in a 60–99 years-old group of moderate-to-severe asthmatics, found critical errors in 31.5% of 366 patients using the Diskus® and 66% of 414 using the Turbohaler®.

In the literature there is not agreement on the situations which predispose to inhaler misuse. We have observed the strongest associations between inhaler misuse and age, level of education and amount and quality of instruction received for good inhaler technique. In a multicentre study including 1305 experienced outpatients with asthma and COPD carried out in 2001–2002, we had found these same associations.[27] We would like to stress the role of instruction by health caregivers for reducing inhaler mishandling, as it is the only modifiable factor (and independently of the used device!) among those observed. It has been suggested[28] that patients using two or more different devices are predisposed to inhaler misuse as compared to those with only one type of inhaler, but we did not confirm this finding after adjustment for age.

As already observed, our study has some limitations. Firstly, our findings on inhalation technique may be biased by the choice of criteria to define the mishandling for each device. Secondly, our findings were based on investigators' judgments and, although we attempted to co-ordinate these observations, they have a subjective basis. However, it is noteworthy that the finding of inhaler mishandling judged on a clinical basis was associated with poor disease control and increased health care resources use. Little information was previously available about the outcomes of inhaler misuse. In a large study including 4078 subjects using ICS via CFC–MDIs, an association between inhaler mishandling and uncontrolled asthma was observed.[3] On the contrary, the correction of MDIs misuse by health caregivers education improved quality of life in 69 asthmatics.[29] Another randomized controlled study with 48 COPD or asthmatic patients using DPIs reported subjective improvements in breathlessness after inhaler training, but no objective measure was recorded.[30] At last, a controlled study including 97 asthmatics who at baseline was respectively 7% and 13% of Turbuhaler® and Diskus® users with good inhaler technique obtained an improvement in quality of life after a training intervention on inhaler technique, although the details of mishandling were not described.[31] Our findings confirm and enlarge these previous studies, showing that inhaler mishandling is not only a wasting, but may have relevant clinical consequences in terms of unscheduled health-care resource use and disease control. The relationship between inhaler misuse and disease control measured by ACT score was significant for both the asthmatic group alone and the whole population. Although the ACT is not devised to ascertain COPD control, items evaluating chronic phlegm, episodes of breathlessness, increased use of relievers, sleep disturbances and everyday limitation may possibly be considered as indices of instability even for COPD patients. Furthermore, the association between poor clinical control and frequency of critical errors with inhalers in an observational study does not automatically mean that a better inhalation technique would

necessarily improve clinical control. Several other reasons may contribute to poor disease control, such as patients with poor inhalation technique could also be non-adherent to drug prescriptions or lead uncorrected lifestyle.

In conclusion, this study shows that mishandling of inhaler technique remains common in real life for both MDIs and DPIs and is associated with poor clinical control and increased unscheduled health-care resources in asthma and COPD patients. Further prospective studies are needed to assess the value of educational interventions in patients showing poor inhalation technique and whether improvements in inhalation technique might be related to better disease control and clinical outcomes.

## Conflict of interest

The study was supported from Chiesi, which does not interfere with the study design, analysis and interpretation of the results and writing of the manuscript.

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## Appendix

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## Supplementary material

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## References

1. Saunders KB. Misuse of inhaled bronchodilator agents. *BMJ* 1965;**1**:1037—8.
2. Lindgren S, Bake B, Larsson S. Clinical consequences of inadequate inhalation technique in asthma therapy. *Eur J Respir Dis* 1987;**70**:93—8.
3. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J* 2002;**19**:246—52.
4. Lavorini F, Magnan A, Dubus JC, et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. *Respir Med* 2008;**102**:593—604.
5. Melani AS, Zanchetta D, Barbato N, et al. Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. *Ann Allergy Asthma Immunol* 2004;**93**:439—46.
6. Epstein S, Maidenberg A, Hallett D, Khan K, Chapman KR. Patient handling of a dry-powder inhaler in clinical practice. *Chest* 2001;**120**:1480—4.
7. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;**113**:59—65.
8. Mahler D, Wells C. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;**93**:580—5.
9. Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. *Eur Respir J* 1993;**16**(Suppl. 6):5—40.
10. Newman SP. Inhaler treatment options in COPD. *Eur Respir Rev* 2005;**14**:102—8.
11. Chapman KR, Love L, Brubaker H. A comparison of breath-actuated and conventional metered-dose inhaler inhalation techniques in elderly subjects. *Chest* 1993;**104**:1332—7.
12. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices. *Respir Med* 2000;**94**:496—500.
13. Engel T, Scharling B, Skovsted B, Heinig JH. Effects, side effects and plasma concentrations of terbutaline in adult asthmatics after inhaling from a dry powder inhaler device at different inhalation flows and volumes. *Br J Clin Pharmacol* 1992;**33**:439—44.
14. Newman SP, Hollingworth A, Clark AR. Effect of different modes of inhalation on drug delivery from a dry powder inhaler. *Int J Pharm* 1994;**102**:127—32.
15. McFadden ER. Improper patient technique with metered dose inhalers: clinical consequences and solutions to misuse. *J Allergy Clin Immunol* 1995;**96**:278—83.

16. Thorsson L, Edsbäcker S. Lung deposition of budesonide from a pressurized metered-dose inhaler attached to a spacer. *Eur Respir J* 1998;**12**:1340—5.
17. Newman SP, Pavia D, Garland N, Clarke SW. Effects of various inhalation modes on the deposition of radioactive pressurized aerosols. *Eur J Respir Dis* 1982;**119**(Suppl. 63):57—65.
18. Newman SP, Weisz AWB, Talaee N, Clarke SW. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax* 1991;**46**:712—6.
19. Hindle M, Newton DAG, Chrystyn H. Investigations of an optimal inhaler technique with the use of urinary excretion as a measure of relative bioavailability to the lung. *Thorax* 1993;**48**:607—10.
20. Farr SJ, Rowe AM, Rubsamen R, Taylor G. Aerosol deposition in the human lung following administration from a microprocessor controlled pressurised metered dose inhaler. *Thorax* 1995;**50**:639—44.
21. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Influence of particle size and patient dosing technique on lung deposition of HFA-beclomethasone from a metered dose inhaler. *J Aerosol Med* 2005;**18**:379—85.
22. Serra-Batlles J, Plaza V, Badiola C, Morejon E. Patient perception and acceptability of multidose dry powder inhalers: a randomized crossover comparison of diskus/accuhaler with turbuhaler. *J Aerosol Med* 2002;**15**:59—64.
23. Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. *J Aerosol Med* 2003;**16**:249—54.
24. Melani AS, Bracci LS, Rossi M. Reduced peak inspiratory effort through the Diskus® and the Turbuhaler® due to mishandling is common in clinical practice. *Clin Drug Invest* 2006;**25**:543—9.
25. Nsour WM, Alldred A, Corrado OJ, et al. Measurement of peak inhalation rates with an in-check meter® to identify an elderly patient's ability to use a Turbuhaler®. *Respir Med* 2001;**95**: 965—8.
26. Kamin WES, Genz T, Roeder S, et al. The inhalation manager: a new computer-based device to assess inhalation technique and drug delivery to the patient. *J Aerosol Med* 2003;**16**:21—9.
27. Sestini P, Cappiello V, Aliani M, et al., on behalf of the Associazione Italiana Pneumologi Ospedalieri (AIPO) Educational Group. Prescription bias and factor associated with improper use of inhalers. *J Aerosol Med* 2006;**19**:127—36.
28. van der Palen J, Klein JJ, van Herwaarden CLA, Zielhuis GA, Seydel ER. Multiple inhalers confuse asthma patients. *Eur Respir J* 1999;**14**:1034—7.
29. Al-Showair RAM, Pearson SB, Chrystyn H. The potential of a 2Tone trainer to help patients use their metered-dose inhalers. *Chest* 2007;**131**:1776—82.
30. Verver S, Poelman M, Bogels A, Chisholm SL, Dekker FW. Effects of instruction by practice assistants on inhaler technique and respiratory symptoms of patients. A controlled randomized videotaped intervention study. *Fam Pract* 1996;**13**:35—40.
31. Basheti IA, Armour CL, Bosnic-Anticevich SZ, Reddel HK. Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. *Respir Care* 2008;**72**:26—33.