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ORIGINAL ARTICLE
COPD

Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients

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ABSTRACT Acute exacerbations of chronic obstructive pulmonary disease (COPD) can be prevented by inhaled treatment. Errors in inhaler handling, not taken into account in clinical trials, could impact drug delivery and minimise treatment benefit. We aimed to assess real-life inhaler device handling in COPD patients and its association with COPD exacerbations.

To this end, 212 general practitioners and 50 pulmonologists assessed the handling of 3393 devices used for continuous treatment of COPD in 2935 patients. Handling errors were observed in over 50% of handlings, regardless of the device used. Critical errors compromising drug delivery were respectively made in 15.4%, 21.2%, 29.3%, 43.8%, 46.9% and 32.1% of inhalation assessment tests with Breezhaler® (n=876), Diskus® (n=452), Handihaler® (n=598), pressurised metered-dose inhaler (pMDI) (n=422), Respimat® (n=625) and Turbuhaler® (n=420).

The proportion of patients requiring hospitalisation or emergency room visits in the past 3 months for severe COPD exacerbation was 3.3% (95% CI 2.0–4.5) in the absence of error and 6.9% (95% CI 5.3–8.5) in the presence of critical error (OR 1.86, 95% CI 1.14–3.04, p<0.05).

Handling errors of inhaler devices are underestimated in real life and are associated with an increased rate of severe COPD exacerbation. Training in inhaler use is an integral part of COPD management.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death in most industrialised countries. Exacerbation of COPD is an acute event characterised by a worsening of the patient's respiratory symptoms. Severe exacerbations lead to emergency visits and hospital admissions and are associated with increased mortality. The goals of treatment for COPD exacerbations are to minimise the impact of the current exacerbation and prevent the development of subsequent exacerbations [1]. Based on large number of randomised control trials [2–6], inhaled long-acting bronchodilators, beta-agonists and/or muscarinic antagonists associated or not with inhaled steroids have been recommended in treatment guidelines to prevent COPD exacerbations [1]. All these trials included patients trained in the correct use of the inhalers. In real life, correct use of the inhalation devices is essential to ensure the effectiveness of the treatment [1]. A high rate of inhalation device mishandling has been reported in younger asthma patients, with an impact on asthma control [7–9]. COPD patients are often elderly, have a low inspiratory capacity and require devices that are easy to use and to inhale through even with a low flow rate [10], and yet the rates of inhaler device mishandling and their potential impact on COPD exacerbation are not known [1, 11].

The aim of our study was to evaluate with general practitioners (GPs) and pulmonologists the real-life handling of the most frequently prescribed inhalation devices used for continuous treatment of COPD and the clinical impact of handling errors on COPD exacerbation rate.

Methods

GPs and pulmonologists were recruited to participate in the study using paper mail (n=13 023) or emails (n=27 763) sent to all non-hospital-based pulmonologists and a random sample of GPs. They were asked to recruit patients above the age of 40 years, current or ex-smokers of ⩾10 pack-years, who had been using an inhaler device for more than 1 month for continuous treatment of COPD.

Physicians asked their COPD patients using any of the six most common inhalers to come to the next visit with their own inhaler. They were requested to take a puff of their usual inhaler with their usual inhalation technique, which was observed and rated by the physician. Physicians were asked not to give any instructions before the test and to pay attention particularly to dose preparation and delivery.

Measurement

Physician received up to two study packs containing 11 questionnaires and package leaflets for each inhaler, approved by the European Medicines Agency (EMA). Physicians were instructed to complete at least five case report forms with items on patient characteristics, COPD history, COPD exacerbations and treatments in the past 3 months. Assessment of patient handling of their own device was standardised using a checklist of the key features of the inhalation technique (scored "yes", "no", "don't know") established for each inhaler from the package leaflet.

Analyses

Some errors were considered device independent: no exhalation before inhalation, inspiration through the nose or not holding the breath a few seconds after inhalation. Other errors were considered device dependent. Errors were considered critical if they could have substantially affected dose delivery to the lungs. These critical errors were defined prior to the study by an expert committee and not revealed to the participating physicians before the study. These included lack of inhalation through the mouthpiece for all devices, blowing in the device before inhalation for dry powder inhalers, and for:

1. Breezhaler®: failure to insert capsule, failure to press and release buttons, powder remaining in the capsule by the end of inhalation
2. Diskus®: failure to slide the lever, manoeuver despite no dose remaining on the dose counter
3. Handihaler®: opening the next dose blister, failure to insert capsule, failure to press and release buttons, powder remaining in the capsule by the end of inhalation
4. pMDI: poorly synchronised hand actuation and inhalation
5. Respimat®: lack of cartridge in the device, manoeuver despite no dose remaining on the dose counter, failure twisting the base, poorly synchronised hand actuation and inhalation
6. Turbuhaler®: failure to hold the inhaler upright when twisting the grip (tolerance ±45°), missing rotating grip clockwise then anticlockwise until "click", manoeuver despite no dose remaining on the dose counter.

Because the inhalation flow and duration in this large real-life study could not be measured, inhalation parameters were not included in critical error definitions.

COPD exacerbations in the previous 3 months and their association with handling errors were studied in patients who had had continuous treatment with the tested inhaler for more than 3 months. Moderate

exacerbation was defined as an exacerbation requiring antibiotics and/or oral steroids; severe exacerbation was defined as an exacerbation requiring hospitalisation or an emergency room visit.

In this observational study, the number of devices assessed was set to ensure a minimal precision of 5% for a proportion of critical errors ranking from 10% to 50%. With 384 handling evaluations per device, the precision of measure ranged from 3% for 10% critical errors to 5% for 50% critical errors. To ensure a sufficient number of newer and of less-prescribed devices, the number of inhaler questionnaires within each study pack was based on the relative prescription of each device according to French 2014 market share (three questionnaires if market share was <10% (Breezhaler® and Respimat®), two questionnaires if market share was 10–20% (Handihaler®), one questionnaire if market share >20% (Diskus®, pMDI and Turbuhaler®)).

All data were recorded prospectively in a database constructed using Grails (version 2.2.4). Analyses were conducted using SAS® software (SAS Institute, version 9.4, NC, USA).

Descriptive analyses were done for each device, expressed as the frequency and percentage for qualitative variables and as the arithmetic mean, SD, median with interquartile ranges and minimum–maximum range for quantitative variables. A significance level of 5% was adopted for statistical analyses; 95% confidence intervals of proportions were estimated by normal approximation, exact binomial approximation (if n<100 patients) or the Poisson method (if n⩾100 patients and k<15 events).

Dunnett *post hoc* test and univariate logistic regression were used to compare continuous and qualitative characteristics between error type groups, with "no error" as reference.

A multiple binary logistic regression model was used, restricted to patients treated for at least 3 months with the device, to assess the determinants of severe exacerbation in the past 3 months. The independent variables tested in the model were sex, age (⩽70 years, >70 years), previous asthma (yes, no), duration of COPD (⩽5 years, 6–10 years, >10 years), error type (no error, non-critical error(s), at least one critical error), duration (in months) of device use (3–6, 6–12, 12–24, 24–36, 36–60, ⩾60), severity (forced expiratory volume in 1 s (FEV_1)), tobacco use (active, previous), poor adherence defined by more that 2 days off treatment in the previous 7 days (no, yes) and device tested.

The modelling strategy for the selection of variables to be included in the final model was a backward elimination method (significance set at 5%) with all candidate variables associated with the variable of interest in the univariate analysis (p set at 0.25). Confounding, interactions and multicollinearity between all variables retained in the univariate analysis were also tested. The association with the dependent variable was expressed with odds ratio, associated 95% confidence interval, and Wald test p value. A model's goodness-of-fit was assessed with Hosmer and Lemeshow's test and its discriminant performance with area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

This non-interventional study was approved by the institutional committees in charge of data protection in biomedical research in France (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS), Commission Nationale de l'Informatique et des Libertés (CNIL)). An information sheet was provided to patients. The study was registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) e-register at the EMA (www.encepp.eu).

Results

In total, 212 GPs and 50 pulmonologists participated in this study (mean age 52.8 years) and returned 3393 device-handling questionnaires (876 Breezhaler®, 452 Diskus®, 598 Handihaler®, 422 pMDI, 625 Respimat® and 420 Turbuhaler®) from 2935 patients. Patient characteristics are summarised in table 1.

Whatever the device studied, <40% of patients were able to perform a perfect inhalation according to the package instructions leaflet (table 2). The most common errors were failure to breathe out before actuation (22.5%), inhalation through the nose (22.2%) and not holding breath a few seconds after inhalation (26.9%). These errors were considered as device-independent and observed in 50.9–56.8% of the patients with no difference between inhalation devices.

Patients made critical errors in 15.4%, 21.2%, 29.3%, 32.1%, 43.8% and 46.9% of handlings with Breezhaler®, Diskus®, Handihaler®, Turbuhaler®, pMDI and Respimat® respectively. Critical errors were more frequent with non-breath-actuated devices (pMDI and Respimat®), mainly due to poor hand–lung synchronisation. Critical errors due to dose preparation were more frequent with Respimat® (no cartridge in the device, inhalation with dose counter at zero, error in twisting the base or pressing the button) or Turbuhaler® (dose counter at zero, twisting the base with a device in horizontal position or failure to twist the base in both directions before use) (table 3).

Critical error rate was no different between patients visiting GPs (30.6%, 95% CI 28.8–32.4) and pulmonologists (28.0%, 95% CI 24.7–31.2). Inhalation technique was reported with no error in 25.4% (95% CI 23.8–27.1)

TABLE 1 Patient characteristics

	Breezhaler®	Diskus®	Handihaler®	pMDI	Respimat®	Turbuhaler®	Total[#]
Number of patients n	876	452	598	422	625	420	2935
Male/female %	66.2/33.8	60.0/40.0	68.9/31.1	57.8/42.2	63.0/37.0	61.1/38.8	63.2/36.8
Age years							
Mean±SD	65.9±11.1	65.4±11.5	66.5±10.8	64.5±11.9	65.9±11.5	65.5±11.9	65.4±11.4
(min–max)	(41–97)	(41–96)	(41–92)	(41–99)	(41–98)	(41–94)	(41–99)
Tobacco							
Current/ex-smoker %	39.6/60.3	37.8/62.2	38.5/61.5	36.5/63.5	37.8/62.2	41.4/58.6	39.1/60.8
Pack-year mean±SD	34±17	31±15	33±15	31±17	32±15	31±16	32±16
Positive asthma history %	20.8	33.0	23.1	37.2	21.8	29.5	26.4
Previous spirometry n (%)	546 (62.3)	281 (62.2)	397 (66.4)	253 (60.0)	372 (59.5)	251 (59.8)	1733 (59.0)
FEV_1 %							
⩾80%	19.4	14.9	17.9	17.4	20.2	17.1	19.0
50 to <80%	56.0	61.6	50.9	53.8	59.9	57.8	57.7
30 to <50%	19.4	16.0	24.2	19.8	15.9	19.5	17.9
<30%	3.1	5.7	4.3	4.7	2.4	3.6	2.9
ND	2.0	1.8	2.8	4.3	1.6	2.0	2.5
Education %							
Demonstration of use	88.5	84.1	84.6	82.2	88.3	84.0	85.9
Leaflet read at least once	59.0	58.8	58.9	56.6	63.7	60.0	59.7
Poor adherence previous week %	10.4	4.0	11.9	3.8	10.9	4.3	8.3

pMDI: pressurised metered-dose inhaler; FEV_1: forced expiratory volume in 1 s; ND: no data. [#]: patients can use more than one device, so the total is not the sum of individual values.

and 24.6% (95% CI 21.5–27.7) of patients seen by GPs and pulmonologists respectively. Patients with critical errors were more likely to have had fewer demonstrations of use, less leaflet reading, lower efficacy perception or lower perfect adherence in the last week (table 4).

In patients treated for at least 3 months (n=2760), the percentage of patients experiencing a moderate to severe exacerbation varied by device by 30.8–45% and a severe exacerbation by 3.4–7.3%. The rate of severe exacerbations in the past 3 months doubled between patients with no error (3.3%, 95% CI 2–4.5) and patients with at least one critical error (6.9%, 95% CI 5.3–8.5).

The occurrence of severe exacerbations of COPD in patients treated for at least 3 months with a tested device was significantly associated with critical errors, previous asthma, duration of COPD, age and poor adherence (table 5). Duration of device use, sex and tobacco use were not associated with severe exacerbations ($p>0.25$) and removed from the model after verifying these were not confounding variables. FEV_1, measured in only 59% of patients in this real-life study, could not be included in the model without removing 41% of the patients. We performed a linear regression showing that duration of COPD was associated with FEV decline ($p<0.0001$). Duration of COPD could thus be considered as a proxy of severity included in the model. Despite a non-statistically significant effect of device type on the severe exacerbation rate, we have forced this variable in the logistic regression model to adjust results on. The final model showed a good model fit (Hosmer–Lemeshow test p=0.7978) and a good discriminant power (ROC AUC=0.72).

Discussion

This study demonstrates that device-handling errors including critical errors rates are particularly high in COPD patients and that these errors are associated with severe COPD exacerbations. Three main conclusions

TABLE 2 Error summary by system

	Breezhaler®	Diskus®	Handihaler®	pMDI	Respimat®	Turbuhaler®	Total[#]
Devices n	876	452	598	422	625	420	3393
No error	36.5 (33.3–39.7)	29.2 (25.0–33.4)	10.7 (8.2–13.5)	16.4 (12.8–19.9)	23.0 (19.7–26.3)	30.5 (26.1–34.9)	25.3 (23.6–26.7)
Device-independent errors	53.5 (50.2–56.8)	50.9 (46.3–55.5)	54.8 (50.9–58.8)	53.8 (49.0–58.5)	56.8 (52.9–60.7)	51.9 (47.1–56.7)	53.8 (52.2–55.5)
Device-dependent errors	15.4 (13.0–17.8)	29.2 (25.0–33.4)	75.3 (71.8–78.7)	70.1 (65.8–74.5)	50.6 (46.6–54.5)	32.1 (27.7–36.6)	43.1 (41.5–44.8)
At least one critical error	15.4 (13.0–17.8)	21.2 (17.5–25.0)	29.3 (25.6–32.9)	43.8 (39.1–48.6)	46.9 (43.0–50.8)	32.1 (27.7–36.6)	30.0 (28.5–31.6)

Data are presented as % (95% CI), unless otherwise indicated. pMDI: pressurised metered-dose inhaler. [#]: total number of evaluated devices.

TABLE 3 Critical error descriptions

	Breezhaler®	Diskus®	Handihaler®	pMDI	Respimat®	Turbuhaler®
Devices n	876	452	598	422	625	420
Dose preparation critical errors						
Lack of cartridge or no capsule in device prior to inhalation	3 (0.3)		5 (0.8)		35 (5.6)	
Inhalation despite dose counter at zero		20 (4.4)			37 (5.9)	16 (3.8)
Opening next blister when taking the capsule			34 (5.7)			
Activation error (not pressing button, twisting error, loading position error, not sliding lever, opening mouthpiece)	4 (0.5)	9 (2.0)	18 (3.0)		7 (1.1)	86 (20.5)
Total dose preparation critical error [95% CI]	7 (0.8) [0.3–1.6]	29 (6.4) [4.2–8.7]	48 (8.0) [5.8–10.2]	–	78 (12.5) [9.9–15.1]	100 (23.8) [19.7–27.9]
Dose delivery critical errors						
Expiration in powder device prior inhalation	87 (9.9)	60 (13.3)	60 (10.0)			36 (8.6)
No inspiration through the mouthpiece	21 (2.4)	15 (3.3)	22 (3.7)	7 (1.7)	11 (1.8)	14 (3.3)
Remaining powder in the capsule by the end	33 (3.8)		80 (13.4)			
Lack of synchronisation hand–lung with smoke emanation				181 (42.9)	246 (39.4)	
Total dose delivery critical error [95% CI]	131 (15.0) [12.6–17.3]	70 (15.5) [12.2–18.8]	149 (24.9) [21.4–28.4]	185 (43.8) [39.1–48.6]	249 (39.8) [36–43.7]	48 (11.4) [8.4–14.5]

Data are presented as n (%), unless otherwise indicated. pMDI: pressurised metered-dose inhaler.

can be drawn from our results. First, the results of clinical trials done in trained subjects might not translate in real life in patients with poor training and many handling errors. The population benefits expected from the clinical trials of such treatments would not materialise in real life.

Second, training patients in the use of the inhaler devices is a crucial aspect of treatment efficacy, and prescribers or health professionals should regularly verify the patients' proficiency in the use of treatment. For orally given medicines, use training is easy, most people know how to swallow a tablet. Using these inhalators is more complex and requires the understanding and proper execution of a complex chain of actions, including breath control and breath–hand coordination, especially for the devices that are not breath-actuated, and the ability to arm the device and make certain it is loaded. Training must be emphasised as a crucial part of treatment, and must be amenable to patients and involve all healthcare professionals involved in the care of the patient.

Third, beyond patient training, there is no perfect device and more research is needed by device manufacturers to make these devices more error-safe and even easier to use.

Device-handling errors have already been described in asthma, as well as their association with poor disease control [12]. The association we found between critical errors and severe COPD exacerbations was

TABLE 4 Description of patients according to the occurrence of errors

	No error	Non-critical error	p value	Critical error	p value
Errors n	857	1236		1019	
Age years (mean±SD)	64.8±11.3	66.1±11.1	<0.05	65.7±11.7	ns
Male/female %	63.5/36.5	64.3/35.7	ns	62.3/37.7	ns
Mean duration of use of the device months (mean±SD)	31.9±36.1	39.1±44.9	<0.001	39.5±44.8	<0.001
Demonstration of use at least once	90 (88.0–92.0)	85.4 (83.4–87.3)	<0.01	83.6 (81.3–85.9)	<0.0001
Reading of leaflet at least once	69.1 (66.0–72.2)	58.7 (56.0–61.5)	<0.0001	53.9 (50.8–56.9)	<0.0001
Poor adherence	4.4 (3.1–5.8)	8.0 (6.5–9.5)	<0.01	12.6 (10.5–14.6)	<0.0001
Treatment perceived very efficacious	40.4 (37.1–43.7)	28.8 (26.3–31.4)	<0.0001	27.8 (25.1–30.6)	<0.0001
Moderate to severe[#] exacerbation in past 3 months[¶]	32.1 (28.9–35.4)	35.6 (32.9–38.4)	ns	38.5 (35.4–41.5)	<0.01
Severe exacerbation[+] in past 3 months[¶]	3.3 (2.0–4.5)	4.6 (3.4–5.8)	ns	6.9 (5.3–8.5)	<0.01

Data are presented as % (95% CI), unless otherwise indicated. ns: non-significant. [#]: exacerbation with antibiotherapy, corticotherapy, emergency room visit or hospitalisation; [¶]: restricted to patients treated for at least 3 months with the device (no error n=794; non-critical error n=1153; critical error n=975); [+]: exacerbation with emergency room visits or hospitalisation.

TABLE 5 Determinants of severe exacerbation in the past 3 months among patients treated for at least 3 months (multiple binary logistic regression: final model)

	Severe exacerbation in the past 3 months			
	No	Yes	OR (95% CI)[#]	p value
Subjects n	2775	146		
Error				0.0297
No error	767 (96.7)	26 (3.3)	1	
Non-critical error(s)	1100 (95.4)	53 (4.6)	1.29 (0.79–2.11)	
At least one critical error	908 (93.1)	67 (6.9)	1.86 (1.14–3.04)	
Age				0.0053
⩽70 years	1848 (96.3)	72 (3.7)	1	
>70 years	927 (92.6)	74 (7.4)	1.65 (1.16–2.36)	
Previous asthma				0.0034
No	2058 (95.7)	93 (4.3)	1	
Yes	717 (93.1)	53 (6.9)	1.72 (1.20–2.46)	
Duration of COPD				<0.0001
⩽5 years	891 (98.8)	11 (1.2)	1	
6–10 years	703 (95.1)	36 (4.9)	4.03 (2.03–8.01)	
>10 years	1181 (92.3)	99 (7.7)	5.77 (3.03–10.96)	
Poor adherence				0.0451
No	2550 (95.3)	127 (4.7)	1	
Yes	236 (92.9)	18 (7.2)	1.73 (1.01–2.97)	

Data are presented as n (%), unless otherwise indicated. COPD: chronic obstructive pulmonary disease. [#]: adjusted by type of inhalation device.

therefore not unexpected. After all, a drug that is not taken (or, in this case, inhaled) will not have the effect that is expected. These drugs and devices have been found to be effective in clinical trials in reducing acute exacerbations. In our study, critical errors resulted in an odds ratio of exacerbations of 1.86. Such a magnitude could negate the benefit of treatment in preventing COPD exacerbation. Mishandling could actually be even more pejorative, leading the prescriber, thinking the device is well used, to increase treatment more than necessary.

Weaknesses of the study

The participation rate of physicians was low, even if the number of device handlings observed was sufficient to make conclusions on error rates and the increased risk of exacerbations. A low participation rate could indicate a selection bias, which could result in underestimation of the actual error rate, resulting in the situation being worse than demonstrated by this study.

The error rate might have been underestimated if the self-selected physicians had a special interest in the treatment of COPD or selected high-performing patients. The reported demonstration of inhaler use to 86% of patients seems particularly high. The non-device-specific error rate was constant over all devices, which does not suggest systematic physician preference for any given device. Assuming that the errors in assessment applied equally to all devices, the relationship between devices would still be preserved. We could not measure the inhalation parameters [13]. This could favour Diskus® and Turbuhaler® devices for which poor inhalation flow cannot be evidenced by smoke emission or powder remaining in the capsule.

Physician self-selection is plausible from the low participation rates. However, many physicians actually refused to participate, citing no time and excess administrative duties, making selection bias less likely. In another study on nonsteroidal anti-inflammatory drugs we had found that there was no selection bias in patients whose prescribers agreed to participate, and those whose prescriber declined to participate [14]. In the present case, selection bias could result in even greater error rates in unselected patients. It is unlikely that it would alter the link between errors and exacerbations. It is therefore possible or likely that the general situation is even worse than what we found.

Strengths

This study was done in unselected and *a priori* untrained GPs and theoretically trained pulmonologists. This allowed us to approach both non-specialists and specialists. There was no clear difference between them, confirming the primary role of the patients in the handling errors. In smaller studies assessment

concerns can be fixed using a video-recorded scoring method [15]. In our study, the number of patients studied by device (420–876) limited the impact of some incorrect assessments. The strength of the study is its real-life countrywide setting, which indicates the magnitude of the issue, even if it might be underestimated.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD, updated 2016) only devoted one sentence to inhalation, stating that it is essential to ensure that inhaler technique is correct and to re-check this at each visit and for each change of inhaler device [1]. The results of our study suggest that the proper use of the system appears at least as important as the choice of treatment and should be considered one of the key elements in COPD management and prevention of exacerbation.

Conclusion

Despite an improvement of inhalation technique with breath-actuated inhalers, patients still make a number of errors, some of which are critical to the efficacy of the inhaled treatment, especially in COPD patients. The breath-actuated inhalers are not equal in real life in the frequency of device-dependent errors and critical errors and this could have an impact on clinical outcomes that cannot be predicted from clinical trials. The treatment must reach the bronchi to be effective. Physicians should focus their efforts more on the patient's ability to properly take their treatment than on the choice of the inhaler characteristics to reduce the frequency of COPD exacerbations.

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