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Does mixing inhaler devices lead to unchecked inhaler technique errors in patients with COPD? Findings from the cross-sectional observational MISMATCH study

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ABSTRACT

Background Patients with chronic obstructive pulmonary disease (COPD) may be prescribed multiple inhalers that require different techniques for optimal performance. Mixing devices has been associated with poorer COPD outcomes suggesting that it leads to inappropriate inhaler technique. However, empirical evidence is lacking.

Aims Compare the nature and frequency of dry powder inhaler (DPI) technique errors in patients with COPD using (1) a single DPI or (2) mixed-devices (a DPI and pressurised metered dose inhaler (pMDI)).

Methods Data from the PIFotal study—a cross-sectional study on Peak Inspiratory Flow in patients with COPD using a DPI as maintenance therapy, capturing data from 1434 patients on demographic characteristics, COPD health status and inhaler technique—were used to select 291 patients using mixed-devices. Frequency matching based on country of residence and DPI device type was used to select 291 patients using a DPI-only for comparison. Predetermined checklists were used for the evaluation of DPI video recordings and complemented with additional errors that were observed in ≥10%. Error proportions were calculated for the (1) individual and total number of errors, (2) number of critical errors and (3) number of pMDI-related errors.

Results The study sample contained 582 patients (mean (SD) age 69.6 (9.4) years, 47.1% female). DPI technique errors were common, but not significantly different between the groups. The majority of patients made at least one critical error (DPI-only: 90.7% vs mixed-devices: 92.8%). Proportions of total, 'pMDI-related' and critical errors did not significantly differ between the groups.

Conclusion The nature and frequency of inhaler technique errors did not substantially differ between patients prescribed with a single DPI and mixed-devices. Currently, 'pMDI-related errors' in DPI use are not accounted for in existing checklists.

Trial registration number ENCEPP/EUPAS48776.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous literature has shown that the effectiveness of inhaler therapy can be adversely affected by sub-optimal inhaler technique. Prescribing multiple inhalers requiring different inhalation technique could worsen this problem and has been associated with worse outcomes in patients with chronic obstructive pulmonary disease (COPD).

WHAT THIS STUDY ADDS

⇒ This study showed that, irrespective of the type of device(s) prescribed, patients with COPD reveal poor dry powder inhaler (DPI) technique in general and are also likely to make inhaler technique errors that are currently not accounted for in DPI-specific checklists.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results from this study provide evidence to support changes to potential refinement of inhaler-specific checklists, as patients with COPD seem to be prone to a mismatch between their inhaler technique and prescribed inhaler device.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common chronic lung disease that is characterised by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities.[1] Pharmacological therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Inhaled drug therapy is the cornerstone of treatment of COPD. However, use of inhaler devices can be challenging, potentially leading to critical errors that can reduce drug delivery to the lungs.[2 3]

Therefore, correct inhaler technique is fundamental for effective therapy in both asthma and COPD.[2–4]

There is a wide range of inhalers for COPD on the market, each with its own required technique. There are three principal types of inhalers, which require differing techniques for optimal performance: dry powder inhalers (DPIs), pressurised metered dose inhalers (pMDIs) and soft mist inhalers (SMIs). While DPIs are breath-actuated, and therefore, require the patient to generate sufficient peak inspiratory flow by inhaling forcefully and rapidly, pMDIs and SMIs are less dependent on a patient's inspiratory ability but require patients to have a proper actuation-inhalation technique, ensuring that actuation follows a slow inhalation (when not using a spacer).[5] There are also substantial differences in dose preparation, for example, suspension pMDIs need to be shaken before dose administration, but shaking a primed DPI may, in some devices, lead to falling out powder and therefore a reduction of administered powder during the inhalation manoeuvre.

Handling errors are likely to increase when patients use a combination of inhalers that require different techniques, yet prescribing both a DPI and a pMDI simultaneously is common in the treatment of COPD.[4] For example, the number of inhaler devices used substantially increased the risk of making 'critical' errors that affected drug delivery in a Swedish real-life population of patients with COPD.[6] Furthermore, a mixture of devices requiring dissimilar techniques has also been associated with worse COPD outcomes (eg, higher rate of exacerbations).[7]

The PIFotal COPD study, a cross-sectional multi-country observational study performed in a primary care setting, made video recordings of the inhaler technique of 1434 patients with COPD when using their DPI.[8] These videos were scored for correctness of the steps required to achieve a good inhaler technique for the specific DPI-device based on device-specific checklists. Within the PIFotal study, specific combinations of errors related to the inhalation manoeuvre (ie, not breathing out to empty the lungs before the inhalation, insufficient inspiratory effort, no breath-hold for at least 6 s after the inhalation) were deemed clinically relevant based on their association with worse health outcomes.[9]

Assessing the handling for individual devices, on the basis of standardised checklists, is primarily focused on ensuring that every step required for delivery of medication is correct. Beyond the bounds of a priori defined errors of interest, it is conceivable that patients may perform actions with a DPI that are part of a pMDI's required technique—and vice versa. Hence, it would be of interest for clinical research/practice to consider all sets of errors that may affect drug delivery but are not accounted for in predetermined checklists. More insights in all potential errors may provide additional guidance for future selection of inhaler devices in these already complex patients.

Therefore, in the current analysis, we aimed to compare the nature and frequency of inhaler technique errors, by describing all errors observed rather than using predetermined checklists, between two groups of patients with COPD using either (1) a single DPI or (2) a combination of a DPI and a pMDI.

METHODS

Data source and permissions

Data from the cross-sectional observational real-world PIFotal COPD study were used.[8 10] These data were collected between October 2020 and May 2021 in 102 sites across five European countries (Greece, the Netherlands, Poland Portugal, Spain) and Australia. The MISMATCH study was conducted according to standards recommended for observational research[11] and the use of the PIFotal COPD data was approved by the PIFotal data governance committee and the Anonymous Data Ethics Protocols and Transparency committee—an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group reviewed and approved the protocol.[12] Patients' consent to use their data for future studies was obtained. The MISMATCH study was registered with the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP/EUPAS48776).[13]

Study design

Two study groups were created with patients that either used a single DPI (ie, 'DPI-only') or used a combination of a DPI and pMDI (ie, 'mixed-devices'). Balanced 1:1 frequency matching was applied based on country of residence, the device-type and the number of doses that can be loaded into the device (single dose capsule vs multiple dose), to minimise the potential confounding effects of these factors on the comparison of the DPI technique errors between the groups.

Inclusion and exclusion criteria

In the PIFotal COPD study, inclusion/exclusion criteria were limited to ensure a real-world setting as much as possible. Participants were included in the analysis if the following criteria were met: a clinical diagnosis of COPD, aged 40 years or older at the time of their PIFotal study visit and treated with a DPI as maintenance therapy for their COPD for at least 3 months. Participants were excluded from the study if they were participating in clinical trials with COPD medication, if they had an exacerbation in the 6 weeks prior to the study visit or if they had a life-threatening disease with a life expectancy <6 months. In the MISMATCH study, only participants were included in the analysis who provided written informed consent for use of their video/data for future research. Therefore, Australian patients were excluded from this analysis.

Table 1 Overview of additional errors supplemented to the prespecified checklist

1.	Patient shook the device (A) before or (B) after priming
2.	Patient exhaled into the device (A) before or (B) after the first inhalation
3.	Patient inhaled unnecessary multiple times through the device (cut-off: capsule DPIs* >2 times; multi-dose DPIs>1 time)
4.	Patient inhaled while pressing the button (applicable for capsule DPIs* and Novolizer/Genuair/Easyhaler)
5.	Patient did not prime the inhaler at all (A) or failed to prime the inhaler correctly (B)†
6.	Patient pressed the button to pierce the capsule multiple (>2) times (applicable to capsule DPIs*)
7.	Patient held the inhaler upside down, or in a position that may lead to the powder falling out after priming
8.	Patient stopped without checking for powder residue at the end of the inhalation (applicable to capsule DPIs*)
9.	Patient covered the air vents while inhaling (applicable for Ellipta, Nexthaler, Spiromax, Forspiro)

*Single dose capsule DPIs in this study: Breezhaler, HandiHaler, Zonda and Cyclohaler.
†See online supplemental table 1 for the device-specific instructions.
DPI, dry powder inhaler.

Inhaler technique

Patients' inhaler technique when using their DPI was observed and documented by video recording which was rated offline for errors by two independent reviewers for correctness. To describe all errors, rather than using predetermined checklists only, a sample of 100 DPI videos was selected from the mixed-devices group to observe all types of inhalation actions that were made and that may affect lung deposition. To account for the variety/number of device-specific inhalation actions, one-third (n=33) of the videos was randomly selected from single-dose capsule-based DPIs while the remainder was randomly selected from the eligible multiple-dose DPIs (n=67). The standard list of device-specific errors (online supplemental table 1) to be scored in the full population was complemented with additional errors that were observed at least in 10% of the patients who were eligible for making that specific error with their device. An overview of all new errors added can be found in table 1.

The device-specific checklists that were added on in this study were based on predefined instruction protocols by the Netherlands Lung Alliance (www.inhalatorgebruik.nl), or, if unavailable, the Aerosol Drug Management Improvement Team (www.inhalers4u.org) We scored whether the error was observed, and each inhaler technique error could therefore either be scored as 'yes' (error) or 'no' (no error), or marked as 'not applicable'.

The reassessment of all videos was done separately by two trained researchers. Differences between the two independent observers were resolved by discussion. Unfortunately, data on the inter-rater reliability were not captured. However, the videos were distributed among assessors and evaluated in batches of approximately 20 videos. When researchers could not reach consensus, a third independent expert arbitrated.

Adherence, health status and exacerbations

Adherence was calculated based on the answers on the 10-item Test of Adherence to Inhalers (TAI-10).[14] Items could be scored 1–5 points each. Only if participants scored the maximum number of points on all items (total 50 points), he or she was considered adherent. The TAI questionnaire has been validated in patients with COPD and asthma and correlated with electronic adherence (≥80%).[14]

COPD-related health status was measured with the 10-item self-administered Clinical COPD Questionnaire (CCQ),[15] consisting of three domains: symptoms, functional status and mental health. The CCQ-score is the mean score of 10 item-scores, where each item is scored on a 7-point Likert scale indicating the severity of symptoms.

Moderate exacerbations were defined as exacerbations treated with oral corticosteroids or antibiotics without hospital admission and severe exacerbations were defined as exacerbations requiring hospital admission.

Statistical analysis

Patient characteristics (including demographic variables, maintenance therapy, comorbidities, COPD-related health status and the number of exacerbations in the past 12 months) and the frequency of all inhaler technique errors were described for the total study population, and the likelihood of making the errors was estimated as an OR comparing frequencies observed in both groups (DPI-only vs mixed-devices).

Moreover, the proportion of errors was calculated and compared between the groups. For this article, the proportions were calculated for (1) the total number of DPI technique errors, (2) the number of 'pMDI-related' errors and (3) the number of 'critical' DPI technique errors while using a DPI (table 2).

For each outcome-predictor combination, a binomial multilevel regression model was fitted, allowing for a random effect at the level of the participant's country of residence (n=5). We corrected for overdispersion in the data by including an observation level random effect.[16] With these models, we estimated the ORs and 95% CIs for error proportions in the mixed-devices group compared with the DPI-only group. The models were weighted for the number of errors that could be made with the used device (ie, denominator of the proportion) and device type (ie, single-dose capsule vs multidose DPI) was added as fixed effect to the model. We estimated the bias potential of candidate confounders by estimating the relative change in coefficient of the fixed effect under study (DPI-only vs mixed-devices group) after adding the candidate

Table 2 Combinations of errors used for the analysis

Proportions	Total no of errors observed/total no of actions observed on the video
(1) Total no of DPI technique errors	Proportion of total potential device-specific errors, as described in table 1 and online supplemental table 1
(2) pMDI-related errors while using a DPI	That is, shaking of the device (1) before or (2) after priming, insufficient inspiratory effort, pressing the button while inhaling.
(3) Critical DPI technique errors	That is, not breathing out before the inhalation, insufficient inspiratory effort, no breath-hold (at least 6 s), as described in Kocks *et al*[9]

DPI, dry powder inhaler; pMDI, pressurised metered dose inhaler.

to the unadjusted model. Candidate confounders were then sorted by bias potential in descending order and included in the model one by one. Whenever the bias was ≥5%, the candidate confounder was retained in the model. An overview of all candidate confounders can be found in online supplemental table 2. Sensitivity analyses were carried out to investigate potential modifying effects of country of residence (eg, due to country-specific guidelines/inhaler instructions) by including it as a fixed effect, as well as an interaction term between country of residence and the fixed effect under study (DPI-only vs mixed-devices group). For the analysis, we used complete cases.

The level of statistical significance was set at $p<0.05$. The sample size was determined by the number of eligible patients in the PIFotal dataset according to the inclusion criteria and by the number of patients who could be matched to a patient in the comparison group.

All statistical analyses were performed in R V.4.0.5 [17] in the Rstudio IDE (V.7.2.576).[18]

Patient and public involvement

No patients were directly involved in the conceptualisation and design of the study. A scientific advisory board has been set up to provide advice on the study protocol, the conduct of the study, statistical analysis and interpretation of the data. All members of the scientific advisory board are distinguished researchers and/or clinicians in the field of respiratory medicine and care for patients with COPD. We plan on sharing our findings with clinicians, patients and the public.

RESULTS

Study population

After applying the inclusion and exclusion criteria, a total of 582 participants with COPD from Greece, the

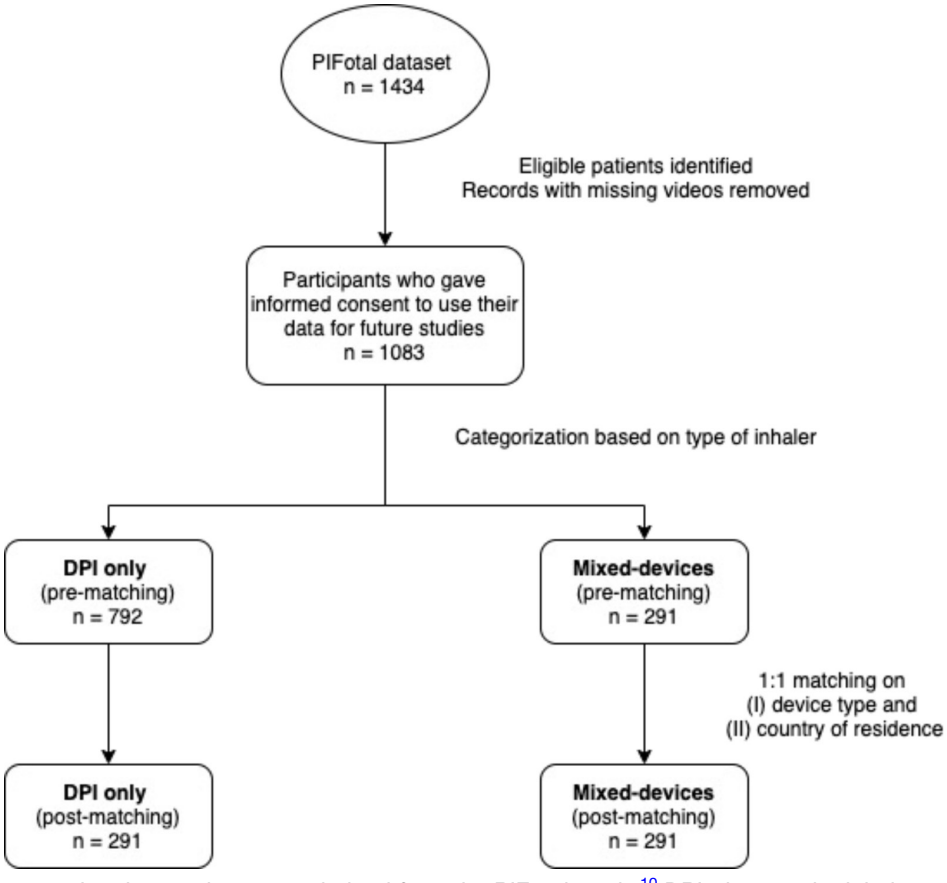

Figure 1 Flow diagram showing study groups derived from the PIFotal study.[10] DPI, dry powder inhaler.

Table 3 Overview of primary dry powder inhalers (DPIs) used for the evaluation of the video recordings

	Overall (n=582)	DPI-only (n=291)	Mixed-devices (n=291)
DPI			
Capsule DPI			
Breezhaler, n (%)	134 (23.0)	66 (22.7)	68 (23.4)
Zonda, n (%)	63 (10.8)	32 (11.0)	31 (10.7)
Handihaler, n (%)	61 (10.5)	32 (11.0)	29 (10.0)
Cyclohaler, n (%)	7 (1.2)	3 (1.0)	4 (1.4)
Multidose DPI	48 (8.2)	19 (6.5)	29 (10.0)
Ellipta, n (%)	118 (20.3)	64 (22.0)	54 (18.6)
Turbuhaler, n (%)	54 (9.3)	27 (9.3)	27 (9.3)
Diskus, n (%)	48 (8.2)	19 (6.5)	29 (10.0)
Genuair, n (%)	32 (5.5)	15 (5.2)	17 (5.8)
Spiromax, n (%)	26 (4.5)	13 (4.5)	13 (4.5)
Nexthaler, n (%)	18 (3.1)	9 (3.1)	9 (3.1)
Easyhaler, n (%)	10 (1.7)	5 (1.7)	5 (1.7)
Forspiro, n (%)	6 (1.0)	3 (1.0)	3 (1.0)
Novolizer, n (%)	5 (0.9)	3 (1.0)	2 (0.7)

Netherlands, Poland, Portugal and Spain were eligible for this study (figure 1). The devices used for the evaluation of the DPI video recordings are shown in table 3. Of these participants, 47.1% were female and the mean (SD) age was 69.6 (9.4) years. The level of COPD airflow obstruction was available for 304 participants and classified as GOLD severity I in 76 (25.0%), II in 150 (49.3%), III in 56 (18.4%) and IV in 22 (7.2%). A capsule DPI as primary inhaler was used in 45.5% of the participants. Participant characteristics are shown in table 4 and online supplemental table 3.

Significant differences (in percentages) between the groups were found in maintenance therapy (eg, more triple therapy in mixed-devices group), years since diagnosis (higher in mixed-devices group), concomitant asthma (more in mixed-devices group), forced expiratory volume in 1 s (lower in mixed-devices group), number of moderate exacerbations in the previous year and CCQ (higher in mixed-devices group) (table 4).

Nature and frequency of inhaler technique errors

In general, the presence and nature of the inhaler technique errors in DPI use was not significantly different between the groups (figure 2).

Additional errors (supplemented to the prespecified checklists, listed in table 1) were common in both group, such as exhaling through the device before (7% in mixed-devices vs 3% in DPI-only group) or after the first inhalation (18% in mixed-devices vs 13% in DPI-only group). Inhaling unnecessarily multiple times through the device was common (19% in mixed-devices vs 16% in DPI-only group). In both groups, more than 60% of the patients with capsule DPIs did not check powder residue at the end of the inhalation, and about 10% of the patients primed the inhaler more times than necessary.

Regarding the critical errors (table 2), 'no breath-hold (at least 6 s)' was more likely to occur in the mixed-devices group (80%) compared with the DPI-only group (70%). The frequency of insufficient inspiratory effort was higher in the mixed-devices compared with the DPI-only group (48% vs 42%), yet without reaching significance. Not breathing out completely before inhalation was observed in more than three-quarters of both the DPI-only and mixed-devices group (77% and 78%, respectively)

The pMDI-related error 'shaking of the device' was more frequently observed before priming (6% in mixed-devices; 3% in DPI-only) than after (2% in mixed-devices, 3% in DPI-only) priming without significant differences between the groups. Pressing the button while inhaling through the device was observed in 11% of the mixed-devices and 8% of the DPI-only group.

Adjusted differences in error proportions between the groups

The total error proportion and the pMDI-related error proportion was not significantly different between the groups (figure 3).

Regarding the proportion of critical errors, 37.5% of patients in the mixed-devices group and 30.2% of patients in the DPI-only group made all the critical errors that could be observed (online supplemental table 4). In the unadjusted analysis (not adjusted for additional confounders), the mixed-devices group were more likely to make a higher proportion of critical errors compared with the DPI-only group (OR 1.34, 95% CI (1.07 to 1.69), p=0.01). The association did not remain significant after

Table 4 Overview of participant characteristics

	Overall (n=582)	DPI-only (n=291)	Mixed-devices (n=291)	P value*
Country of residence				**0.007**
Greece, n (%)	6 (1.0)	3 (1.0)	3 (1.0)	
Poland, n (%)	62 (10.7)	18 (6.2)	44 (15.1)	
Portugal, n (%)	54 (9.3)	33 (11.3)	21 (7.2)	
Spain, n (%)	252 (43.3)	130 (44.7)	122 (41.9)	
The Netherlands, n (%)	208 (35.7)	107 (36.8)	101 (34.7)	
Female				
n (%)	274 (47.1)	135 (46.4)	139 (47.8)	0.803
Age (years)				
Mean (SD)	69.6 (9.4)	70.2 (9.0)	68.9 (9.8)	0.117
GOLD severity				
n (% non-missing)	304 (52.2)	130 (44.7)	174 (59.8)	0.113
I, n (%)	76 (25.0)	38 (29.2)	38 (21.8)	
II, n (%)	150 (49.3)	66 (50.8)	84 (48.3)	
III, n (%)	56 (18.4)	21 (16.2)	35 (20.1)	
IV, n (%)	22 (7.2)	5 (3.8)	17 (9.8)	
FEV_1				
n (% non-missing)	214 (36.8)	90 (30.9)	124 (42.6)	**0.013**
Mean (SD)	62.0 (18.9)	65.7 (18.8)	59.2 (18.6)	
Years since COPD diagnosis				
Mean (SD)	10.4 (8.7)	9.3 (7.9)	11.5 (9.3)	**0.002**
Body mass index (kg/m^2)				
Mean (SD)	27.6 (5.3)	27.3 (4.6)	27.9 (5.9)	0.243
Smoking status				0.184
Current, n (%)	171 (29.4)	90 (30.9)	81 (27.8)	
Former, n (%)	352 (60.5)	178 (61.2)	174 (59.8)	
Never, n (%)	59 (10.1)	23 (7.9)	36 (12.4)	
10-item Test of Adherence to Inhalers (TAI-10)				
n (%)	47.7 (4.6)	47.5 (4.7)	47.9 (4.4)	0.269
Non-adherent to prescribed DPI therapy (TAI-10<50)				
n (%)	242 (41.6)	121 (41.6)	121 (41.6)	1.000
ICS in inhaler				
n (%)	359 (61.7)	184 (63.2)	175 (60.1)	0.495
Maintenance therapy				**<0.001**
Triple therapy, n (%)	130 (22.3)	27 (9.3)	103 (35.4)	
ICS+(LAMA or LABA), n (%)	165 (28.4)	80 (27.5)	85 (29.2)	
LAMA or LABA or ICS mono, n (%)	133 (22.9)	91 (31.3)	42 (14.4)	
LAMA+LABA, n (%)	154 (26.5)	93 (32.0)	61 (21.0)	
Concomitant asthma				
n (%)	93 (16.0)	32 (11.0)	61 (21.0)	**0.002**
Diabetes				
n (%)	126 (21.7)	64 (22.1)	62 (21.3)	0.903
Cardiovascular comorbidity				
n (%)	269 (46.5)	130 (45.0)	139 (47.9)	0.530
Anxiety				
n (%)	135 (23.4)	67 (23.2)	68 (23.5)	1.000
Clinical COPD Questionnaire				

Continued

Table 4 Continued

	Overall (n=582)	DPI-only (n=291)	Mixed-devices (n=291)	P value*
Mean (SD)	1.8 (1.1)	1.5 (1.0)	2.2 (1.1)	**<0.001**
Exacerbations, moderate—no, n (%)				**<0.001**
0, n (%)	427 (73.4)	255 (87.6)	172 (59.1)	
1, n (%)	77 (13.2)	20 (6.9)	57 (19.6)	
2, n (%)	38 (6.5)	10 (3.4)	28 (9.6)	
3, n (%)	16 (2.7)	3 (1.0)	13 (4.5)	
≥4, n (%)	24 (4.1)	3 (1.0)	21 (7.2)	
Exacerbations, severe—no, n (%)				0.632
0, n (%)	560 (96.2)	282 (96.9)	278 (95.5)	
1, n (%)	18 (3.1)	7 (2.4)	11 (3.8)	
2, n (%)	4 (0.7)	2 (0.7)	2 (0.7)	
Years since last inhaler technique instruction				
n (% non-missing)	471 (80.9)	238 (81.8)	232 (80.1)	0.644
Mean (SD)	3.7 (4.1)	3.6 (4.1)	3.8 (4.1)	
Instruction more than 1 year before the visit				
n (% non-missing)	370 (78.6)	190 (79.8)	180 (77.2)	0.690

P<0.05 highlighted in bold.
*P value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's χ^2 test of independent categories, where appropriate.
COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV1, forced expiratory volume in 1 s.

adjusting for potential confounding factors (OR 1.27, 95% CI (0.98 to 1.65), p=0.07, figure 3).

Sensitivity analyses

The OR of making critical errors in the mixed-devices groups as compared with the DPI-only group was significantly (p=0.04) greater in Portugal (OR 2.56, 95% CI (1.07 to 6.10)) than in the other countries (OR 1.24, 95% CI (0.97 to1.60)). The associations for the total errors and pMDI-related errors were not significantly different across the countries.

DISCUSSION

Principal findings

This study in primary care patients with COPD showed that DPI technique errors are common, both in patients using a DPI-only and in patients using mixed-devices. On top of high error frequencies identified based on steps listed on standard checklists, this study demonstrated that patients with COPD—irrespective of whether devices are mixed or not—tend to make errors that are usually not covered by predetermined DPI checklists. Patients with COPD using mixed-devices did not make more errors compared with patients using a single DPI, although the unadjusted analysis showed a higher proportion of 'critical' inhaler technique errors in patients prescribed with mixed-devices as compared with patients using a DPI-only.

Interpretations and comparison with previous studies

The MISMATCH study focused on all actions performed when using a DPI that could potentially affect drug delivery, including actions that are part of the required technique for a pMDI. To this end, inhaler checklists were supplemented with a list of additional errors frequently observed in a subset of 100 video recordings. This data-driven, empirical, approach is unique as most of the currently available literature identified errors solely based on a priori defined, not necessarily data-driven, DPI-specific checklists.[2] The frequency of the additional errors (eg, exhaling through the DPI, multiple inhalations through the device, shaking of the DPI) warrants the need for more awareness among healthcare professionals (HCPs) of these potential device-handling errors and discrepancy between the patients' inhaler technique and the prescribed device. A practical implication of this finding is that during a check-up of inhaler technique, HCPs should be encouraged to ask the patient to demonstrate their day-to-day manoeuvre with their own device (or a placebo-device). This may reveal unexpected handling errors, or those that are not covered by standard checklists, potentially reducing the treatment efficacy. The GOLD guidelines recommend regular inhaler technique assessments, and that it should be part of the management cycle in the adjustment of a patient's pharmacological treatment. In view of this recommendation, it is pivotal to note that 78% of the patients in this study did not receive inhaler technique instructions a year before the study visit. This is a missed opportunity, as previous research showed that a one-time educational

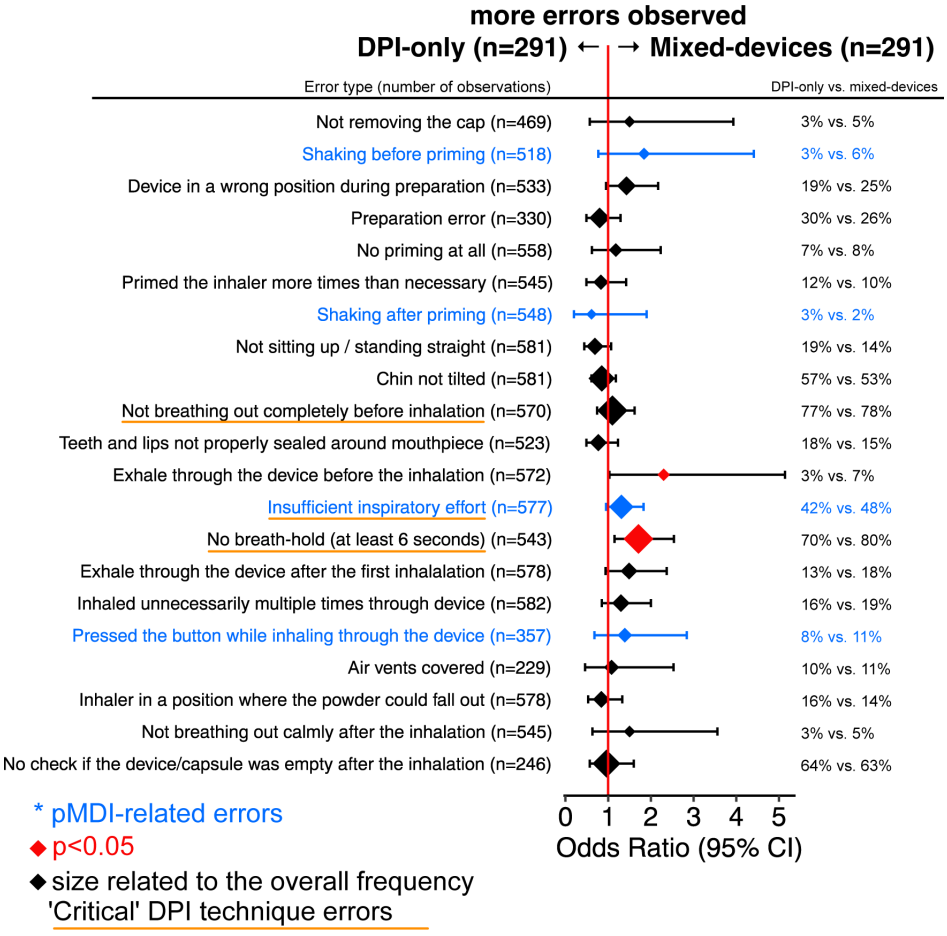

Figure 2 OR (and frequency) of inhaler technique errors in patients with COPD using mixed-devices compared with patients using a DPI only. The size of the rectangle indicates the frequency of the errors. COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; pMDI, pressurised metered dose inhaler.

demonstration and correction of inhaler technique reduces the proportion of patients making inhaler technique errors with a detrimental impact on the delivery of the drug to the lung (eg, incorrect dose preparation and loading), persistent after a follow-up period of 1 year.[19]

There is a wide range of inhalers for COPD on the market, each with its own required technique. Previous studies showed that mixing inhaler devices could lead to more inhaler technique errors due to the confusion and mismatch between inhaler technique instructions between devices.[7 19–22] We could not confirm these results. Evidence showed that patients with asthma using a combination of DPIs were more likely to perform all 'essential' inhaler technique steps correctly compared with patients prescribed with mixed-devices (DPI plus pMDI), 68% vs 54%, respectively. The authors argued that, whenever possible, HCPs should prescribe only one type of inhaler.[23] However, for the DPIs in their study, only two steps of the inhaler technique (correct priming of the device and inhaling forcefully and deeply) were considered, whereas the MISMATCH study focused on all actions that are part of the DPI technique. Another explanation for not confirming these results is that both groups in the current study were matched on the DPI. Device type, rather than the use of multiple inhalers, has been found to be a relevant factor associated with incorrect inhaler technique in patients with COPD.[24] Additionally, it should be acknowledged that information on previous device use was not captured in this study. For instance, it might be that some patients in the DPI-only group previously used another type of device at the time of their diagnosis, such as a pMDI for their rescue medication as needed, but that they switched to a DPI as maintenance therapy when the disease worsened—or that guidelines changed over the years. Previous device prescription may influence the current device handling of the patient and, thus, should be considered when HCPs are trying to select the most appropriate inhaler for the patient with COPD.

Multiple inhaler technique steps may be interrelated and contribute to worse outcomes, as evidenced by the combination of 'critical' errors associated with COPD health status (listed in table 2).[9] Not sufficiently breathing out to empty the lungs before the inhalation may hamper the generation of sufficient inspiratory flow due to lack of inhaled volume[25]—a fundamental step for dose emission since DPIs are flow-dependent. Aforementioned errors may affect the capability for sufficient breath-hold

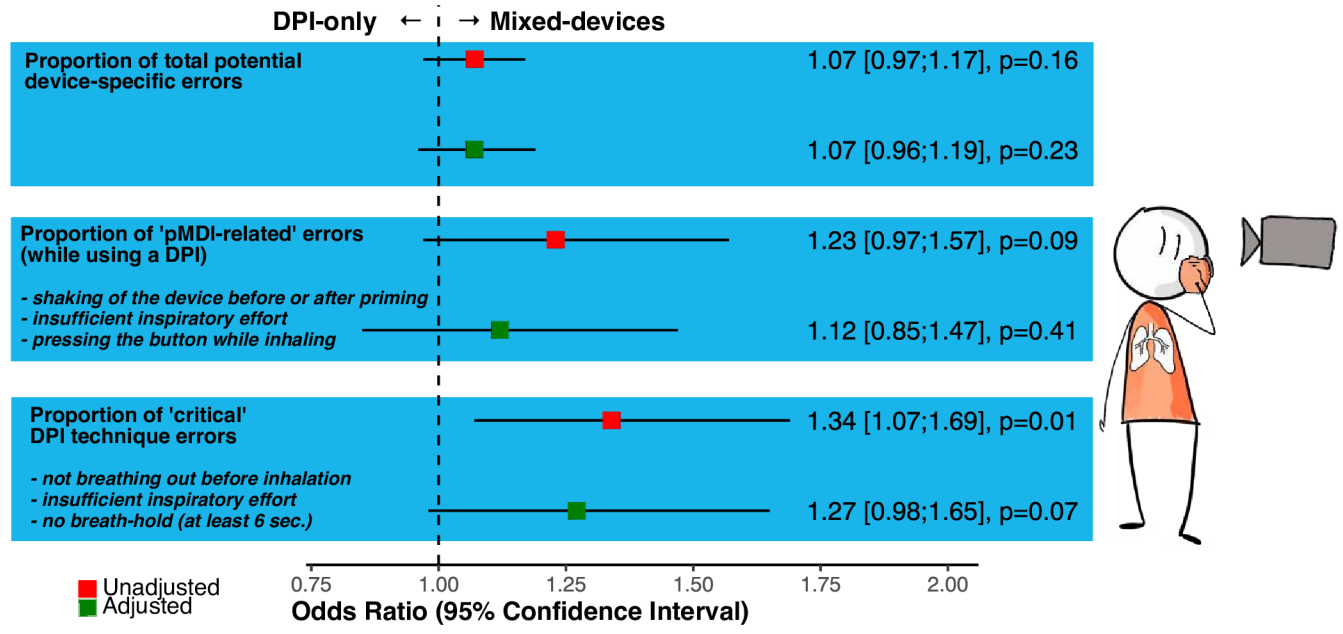

Figure 3 Differences between the groups in the proportion of (1) total number of DPI technique errors, (2) pMDI-related errors while using a DPI and (3) critical DPI technique errors. ORs were adjusted for the following confounders: total errors: concomitant asthma; CCQ; maintenance therapy; body mass index; smoking status; number of moderate exacerbations in the previous year. pMDI-related errors: maintenance therapy; CCQ; smoking status; age. Critical errors: CCQ; maintenance therapy; number of moderate exacerbations in the previous year; smoking status.

time—essential for particles to be deposited in the peripheral areas by sedimentation.[26] The current study observed a tendency towards a higher proportion of these 'critical' errors in the mixed-devices compared with the DPI-only group. A possible explanation of the observed difference is the discrepancy between breathing manoeuvre instructions of DPIs and pMDIs. The generic instruction for DPIs is to inhale as fast and deeply as possible, whereas patients using a pMDI are instructed to breathe in slowly and steadily given that pMDIs are less dependent on a patient's inspiratory ability. However, this finding should be interpreted with caution, as it could—in general—have been biased by the higher disease severity in the mixed-devices group. Increased disease severity has been associated with lower inspiratory muscle strength[27] and reduced peak inspiratory flow[28] in patients with COPD, potentially contributing to the proportion of these 'critical' errors. The same applies to the observed country-specific differences since, in general, Portuguese patients in the mixed-devices group had significantly (p<0.001) worse health status compared with the other countries (mean (SD) CCQ 3.09 (1.26) vs 2.11 (1.08), respectively). The definition of 'critical' errors was based on the association of prespecified inhaler technique errors on COPD health-status,[9] therefore, excluding the list of new 'additional' errors defined in the current study. Future larger studies should investigate whether the additional errors observed in this study are associated with poor COPD outcomes and should be deemed 'critical'.

Another large database study (n=23 494) found that patients using multiple devices were more likely to be non-adherent to their prescribed therapy compared with patients using a single device.[29] This suggests that simpler treatment regimens may be preferred by patients with COPD. In the MISMATCH study, the prevalence of non-adherence (measured with the TAI-questionnaire[14]) did not differ between both groups and was not identified as a relevant confounder in the association with the proportion of errors. With proper inhaler technique as fundamental aspect of medication adherence, this study highlights that an understanding of the patients' day-to-day use and attitudes and beliefs with regard to their inhaler therapy is paramount when selecting the appropriate device for the patient. By using real-time data on inhaler technique, smart inhaler programmes have the potential to optimise self-management, enhance inhaler technique and ultimately improve disease outcomes.[30]

A strength of the MISMATCH study is that it was carried out on a real-life, multinational, COPD patient population, including a variety of DPIs. Furthermore, the results of the data-driven approach provide strong empirical evidence for a set of 'additional' errors that are currently not recognised in inhaler technique checklists. The sensitivity analysis showed that the proportion of errors were not substantially different across the countries, pointing towards the generalisability of the findings. Although this was a post hoc, observational study, a key strength of the study was the matching procedure based on patients' device-type and country of residence. Moreover, the analysis was adjusted for a comprehensive set of potential confounders based on the literature and clinical expertise, such as age[31] and treatment adherence.[32]

Because this study used the video ecordings and data from a previously conducted study, only data collected

at that time were used in the MISMATCH study. Some potential factors may warrant further investigation. First, information about previous device use, years since asthma (or first) diagnosis, and the use of a spacer in combination with a pMDI were not captured. The latter is relevant to clarify some of the errors potentially related to the multiple breath method, such as breathing out through the device after the first inhalation (observed in 18% of mixed-device cluster, figure 2). Second, missing GOLD severity data resulted in an inability to eliminate potential confounding by disease severity—although proxies of disease severity were included in the adjusted models, such as the score on the CCQ and exacerbation rate. We cannot draw any conclusion about a causal effect based on this observational study. However, the use of mixed devices could potentially serve as a proxy for unstable COPD—as indicated by higher CCQ scores compared with DPI-only users, and for instance, the need for pMDI rescue medications. Third, SMIs were not included in the analysis although these devices, in terms of inhaler technique, could be considered rather similar to pMDIs. The low sample (n=35, 2.4%) of patients in the PIFotal dataset using an SMI in combination with their DPI suggested that these patients may had a special indication, which would have been difficult to evaluate. Lastly, the PIFotal study[8] only videorecorded the patients while using their primary DPI. As a potential mismatch between DPI and pMDI instructions could be reciprocal, it would be interesting to investigate whether cross-over effects might be observed when patients in the mixed-devices group use their pMDI—or to compare the mixed-devices group with patients using two or more devices requiring similar inhaler technique (eg, two or more aerosol delivery devices).

Greater emphasis for more careful consideration to be given to the choice of prescribed inhaler devices in COPD has been called for in the literature.[33] The results from this study provide evidence to support changes to potential refinement of inhaler-specific checklists, as patients with COPD seem to be prone to a mismatch between their inhaler technique and prescribed inhaler device. This potential mismatch should be a further consideration when HCPs are prescribing (additional) inhaler therapies.

CONCLUSION

Irrespective of the type of device(s) prescribed, patients with COPD reveal poor DPI technique in general and are also likely to make inhaler technique errors that are currently not accounted for in DPI-specific checklists. Future research is needed to assess the potential impact of these errors on clinical outcomes, as this may help to refine inhaler checklists and could provide additional guidance for device selection in patients with COPD. For optimal COPD treatment in primary care, it is important to assess a patient's inhaler technique, with the optimal checklist, to minimise the potential negative consequences of a mismatch between the patient's technique and their prescribed inhaler(s).

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and the MISMATCH study was conducted according to standards recommended for observational researchand the use of the PIFotal COPD data was approved by the PIFotal data governance committee and the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee—an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group reviewed and approved the protocol. Patients' consent to use their data for future studies was obtained. Participants gave informed consent to participate in the study before taking part.

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REFERENCES

1 2023 GOLD reports - global initiative for chronic obstructive lung disease - GOLD. Available: https://goldcopd.org/2023-gold-report-2/ [Accessed 28 Dec 2022].
2 Usmani OS, Lavorini F, Marshall J, *et al*. Critical Inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respir Res* 2018;19:10.
3 Kocks JWH, Chrystyn H, van der Palen J, *et al*. Systematic review of association between critical errors in inhalation and health outcomes in asthma and COPD. *NPJ Prim Care Respir Med* 2018;28:43.
4 Ahn JH, Chung JH, Shin K-C, *et al*. Critical Inhaler handling error is an independent risk factor for frequent exacerbations of chronic obstructive pulmonary disease: interim results of a single center prospective study. *Int J Chron Obstruct Pulmon Dis* 2019;14:2767–75.
5 Lavorini F, Fontana GA, Usmani OS. New Inhaler devices - the good, the bad and the ugly. *Respiration* 2014;88:3–15.
6 Sulku J, Bröms K, Högman M, *et al*. Critical Inhaler technique errors in Swedish patients with COPD: a cross-sectional study analysing video-recorded demonstrations. *NPJ Prim Care Respir Med* 2021;31:5.
7 Bosnic-Anticevich S, Chrystyn H, Costello RW, *et al*. The use of multiple respiratory Inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. *Int J Chron Obstruct Pulmon Dis* 2017;12:59–71.
8 Leving M, Wouters H, de la Hoz A, *et al*. Impact of PIF, inhalation technique and medication adherence on health status and exacerbations in COPD: protocol of a real-world observational study (Pifotal COPD study). *Pulm Ther* 2021;7:591–606.
9 Kocks J, Bosnic-Anticevich S, van Cooten J, *et al*. Identifying critical inhalation technique errors in dry powder Inhaler use in patients with COPD based on the association with health status and exacerbations: findings from the multi-country cross-sectional observational Pifotal study [Manuscript submitted for publication]. *BMC Pulm Med* 2023;23:302.
10 Kocks JWH, Wouters H, Bosnic-Anticevich S, *et al*. Factors associated with health status and exacerbations in COPD maintenance therapy with dry powder Inhalers. *NPJ Prim Care Respir Med* 2022;32:18.
11 Roche N, Reddel H, Martin R, *et al*. Quality standards for real-world research. focus on observational database studies of comparative effectiveness. *Ann Am Thorac Soc* 2014;11 Suppl 2:S99–104.
12 Respiratory Effectiveness Group (REG). REG research network Organisation. Available: https://www.regresearchnetwork.org/ [Accessed 28 Oct 2022].
13 ENCePP home page. Available: https://www.encepp.eu/ [Accessed 28 Oct 2022].
14 Plaza V, Fernández-Rodríguez C, Melero C, *et al*. Validation of the 'test of the adherence to Inhalers' (TAI) for asthma and COPD patients. *J Aerosol Med Pulm Drug Deliv* 2016;29:142–52.
15 van der Molen T, Willemse BWM, Schokker S, *et al*. Development, validity and responsiveness of the clinical COPD questionnaire. *Health Qual Life Outcomes* 2003;1:13.
16 Harrison XA. Using observation-level random effects to model overdispersion in count data in ecology and evolution. *PeerJ* 2014;2:e616.
17 R Development Core Team. R: a language and environment for statistical computing. R foundation for statistical computing [Vienna, Austria]. 2008. Available: http://www.r-project.org [Accessed 06 Jan 2023].
18 RStudio Team. Rstudio: integrated development environment for R. Boston, MA RStudio, PBC; 2022. Available: http://www.rstudio.com/ [Accessed 06 Jan 2023].
19 Sulku J, Janson C, Melhus H, *et al*. Changes in critical Inhaler technique errors in inhaled COPD treatment - A one-year follow-up study in Sweden. *Respir Med* 2022;197:106849.
20 van der Palen J, Moeskops-van Beurden W, Dawson CM, *et al*. A randomized, open-label, single-visit, crossover study simulating triple-drug delivery with Ellipta compared with dual Inhaler combinations in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2018;13:2515–23.
21 Rootmensen GN, van Keimpema ARJ, Jansen HM, *et al*. Predictors of incorrect inhalation technique in patients with asthma or COPD: a study using a validated videotaped scoring method. *J Aerosol Med Pulm Drug Deliv* 2010;23:323–8.
22 Halpin DMG, Worsley S, Ismaila AS, *et al*. INTREPID: single- *versus* multiple-Inhaler triple therapy for COPD in usual clinical practice. *ERJ Open Res* 2021;7:00950-2020.
23 van der Palen J, Klein JJ, van Herwaarden CL, *et al*. Multiple Inhalers confuse asthma patients. *Eur Respir J* 1999;14:1034–7.
24 Duarte-de-Araújo A, Teixeira P, Hespanhol V, *et al*. COPD: misuse of Inhaler devices in clinical practice. *Int J Chron Obstruct Pulmon Dis* 2019;14:1209–17.
25 Laube BL, Janssens HM, de Jongh FHC, *et al*. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J* 2011;37:1308–31.
26 Hindle M, Newton DA, Chrystyn H. Investigations of an optimal Inhaler technique with the use of urinary salbutamol excretion as a measure of relative bioavailability to the lung. *Thorax* 1993;48:607–10.
27 Kabitz H-J, Walterspacher S, Walker D, *et al*. Inspiratory muscle strength in chronic obstructive pulmonary disease depending on disease severity. *Clin Sci (Lond)* 2007;113:243–9.
28 Leving MT, Kocks J, Bosnic-Anticevich S, *et al*. Relationship between peak Inspiratory flow and patient and disease characteristics in individuals with COPD-A systematic Scoping review. *Biomedicines* 2022;10:458.
29 Yu AP, Guérin A, Ponce de Leon D, *et al*. Therapy persistence and adherence in patients with chronic obstructive pulmonary disease: multiple versus single long-acting maintenance Inhalers. *J Med Econ* 2011;14:486–96.
30 Hoyte FCL, Mosnaim GS, Rogers L, *et al*. Effectiveness of a digital Inhaler system for patients with asthma: a 12-week, open-label, randomized study (Connect1). *J Allergy Clin Immunol Pract* 2022;10:2579–87.
31 Barbara S, Kritikos V, Bosnic-Anticevich S. Inhaler technique: does age matter? A systematic review @ERSpublications The number and type of inhaler errors differs in the elderly, Available: http://ow.ly/9VNH30fFl5Z [Accessed 29 Dec 2022].
32 Price D, Keininger DL, Viswanad B, *et al*. Factors associated with appropriate Inhaler use in patients with COPD – lessons from the REAL survey. *Int J Chron Obstruct Pulmon Dis* 2018;13:695–702.
33 Broeders MEAC, Vincken W, Corbetta L, *et al*. The ADMIT series — issues in inhalation therapy. 7) ways to improve pharmacological management of COPD: the importance of Inhaler choice and inhalation technique. *Prim Care Respir J* 2011;20:338–43.