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Systematic review of the effects of patient errors using inhaled delivery systems on clinical outcomes in COPD

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ABSTRACT

Background Errors using inhaled delivery systems for COPD are common and it is assumed that these lead to worse clinical outcomes. Previous systematic reviews have included patients with both asthma and COPD and much of the evidence related to asthma. More studies in COPD have now been published. Through systematic review, the relationship between errors using inhalers and clinical outcomes in COPD, including the importance of specific errors, was assessed.Methods
Electronic databases were searched on 27 October 2023 to identify cohort, case–control or randomised controlled studies, which included patients with COPD, an objective assessment of inhaler errors and data on at least one outcome of interest (forced expiratory volume in 1 s, (FEV_1), dyspnoea, health status and exacerbations). Study quality was assessed using the Newcastle and Ottawa scales. A narrative synthesis of the results was performed as there was insufficient detail in the publications to allow quantitative synthesis. There was no funding for the review.
Results 19 publications were included (7 cohort and 12 case–control) reporting outcomes on 6487 patients. 15 were considered low quality, and most were confounded by the absence of adherence data. There was weak evidence that lower error rates are associated with better FEV_1, symptoms and health status and fewer exacerbations. Only one considered the effects of individual errors and found that only some were related to worse outcomes.
Conclusion Evidence about the importance of specific errors using inhalers and outcomes would optimise the education and training of patients with COPD. Prospective studies, including objective monitoring of inhalation technique and adherence, are needed.
PROSPERO registration number CRD42023393120.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have shown a relationship between patient errors using inhalers and worse clinical outcomes, but most of this evidence was obtained from patients with asthma and the effect of specific errors has not generally been considered. To our knowledge, there are no systematic reviews of the relationship between errors using inhalers and outcomes solely in patients with COPD and none that consider the importance of specific errors.

WHAT THIS STUDY ADDS

⇒ Our systematic review shows that there is only weak evidence to support the assumption that patient errors using inhaled delivery systems lead to worse clinical outcomes in COPD. When considered separately, it appeared that only some errors were linked to worse outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our review shows that better prospective studies examining clinical outcomes in patients with COPD who make fewer errors after training are needed. Ideally such studies should include objective monitoring of inhalation technique and adherence using digital inhalers and examine the effect of specific errors.

INTRODUCTION

Patients with COPD frequently make errors when using devices to deliver inhaled medications.[1] This problem was first recognised soon after hand-held devices were introduced in the 1960s[2] and despite numerous efforts, there has been little change in proportion making errors since then.[1] Common errors with pressurised metered dose inhalers (pMDIs) and slow mist inhalers relate to coordination, poor inspiratory manoeuvre and lack of breath hold,[1 3 4] while incorrect preparation, failure to exhale and perform a forceful, quick and deep inhalation and lack of breath hold were the most common critical errors with dry powder inhalers (DPI).[1 5] It is generally, and reasonably, assumed that if patients are not using their inhaled delivery system correctly, they will not achieve optimal benefit from their medication, and if they make a critical error, by definition[6] they are unlikely to benefit at all.

Previous systematic reviews have examined the relationship between errors in inhaler technique and outcomes in patients with both asthma and chronic obstructive pulmonary disease (COPD).[6 7] Much of the evidence included was about the effects in patients with

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asthma and there was limited evidence specific to COPD, mainly in meeting abstracts and a few peer-reviewed publications. The relative importance of specific errors has not been considered. As more evidence has now emerged, we have performed a systematic review (PROSPERO, CRD42023393120) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] The objectives of this report are twofold: first to consider the impact of inhalation errors on clinical outcomes in COPD, including the importance of specific errors; and second to provide recommendations for future studies.

METHODS

The PubMed, EMBASE, Cochrane and Google Scholar databases were searched according to PRISMA guidelines[8] for articles published between 1 January 1990 and 1 September 2023 that met the following inclusion criteria: the study design was a cohort, case–control study or randomised controlled trial, included patients with COPD, included an objective assessment of errors using inhaler and included data on at least one clinical outcome of interest: forced expiratory volume in 1 s (FEV1), dyspnoea, health status, exacerbations. Additional studies were sought by searching the reference lists of the selected articles. Articles that were reviews, editorials or meeting abstracts were excluded, as were studies not reporting the results separately for patients with COPD. Studies were not restricted by language or geography.

PubMed, EMBASE and Cochrane were searched using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) search strategy for identifying studies including patients with COPD[9] together with iterative combinations of the following keywords including wildcards for plurals and spelling variants were used during the search process: error, mistake, status, control, critical error, inhaler, outcome, exacerbation (see online supplemental material for search strategies).

Google and Google Scholar were searched using the following key terms, in different combinations: 'copd' inhale* (exacerbat* OR outcome* OR control) (error* OR mistake*).

Publication titles and abstracts were then screened, and articles that did not provide information on device errors and outcomes of COPD were excluded. Data were extracted systematically using a predefined extraction template (online supplemental table 1).

Data extraction and quality assessment

The following data were extracted from each publication: study design (prospective cohort, and whether randomised or not, or cross-sectional), whether only COPD patients or both COPD and asthma patients were studied, number of patients with COPD studied, types of inhaler device included in the study, clinical outcomes assessed, duration of follow-up (for cohort studies), summary of relationship between error rates and clinical outcomes. For both the cross-sectional and observational cohort studies, quality was assessed using applicable Newcastle and Ottawa scales.[10]

A narrative synthesis of the results was performed as there was insufficient detail in the publications to allow quantitative synthesis.

Patient and public involvement

None.

RESULTS

A total of 1312 publications met our initial screening criteria (figure 1). An additional seven publications were identified through a manual search. After removing duplicate studies (n=168), 1144 abstracts were examined to assess relevance whether they met the eligibility criteria. 1091 abstracts were eliminated, leaving 55 full-text articles for review in detail. Among these articles, 36 did not contain information about associations between errors and outcomes or were review articles, resulting in a total of 19 publications that were included in this review[5,11–28] (table 1).

Seven prospective cohort studies of relevance were identified,[11,13,16,19,21,24,26] two studies randomised patients to receive inhaler training or not, three also examined the effects of inhaler training but were not randomised and one monitored patients' inhaler use for 3 months.[16] We considered that no conclusions could be drawn from the studies with follow-up of 1 month or less.[21,26] None of the intervention studies examined the outcomes in patients whose technique had improved compared with patients who continued to make errors and follow-up was often incomplete. Only the study by Cushen *et al*[16] included more than 70 patients and was considered of good quality (table 2).

10 retrospective case–controlled studies, reported in 12 publications, compared the characteristics of patients who made and who did not make errors using their inhalers (table 1).[5,12,14,15,17,18,20,22,23,25,27,28] These included larger numbers of patients than the prospective studies. Three publications[23,27,28] reported different outcomes from the same study (The PIFotal COPD study). In all of these studies it is impossible to determine cause and effect, and only the PIFotal COPD study accounted for the effect of adherence.

In many studies, the exacerbation rates were based on patient recall rather than being derived from medical records, and it was not clear how patients were selected for inclusion. Only the PIFotal COPD study[23,27,28] was considered of good quality (table 2).

Effect of errors on lung function

Figure 2 summarises the findings of the studies with regard to the outcomes. Maricoto *et al* showed that FEV_1 improved significantly after training in inhaler use (mean

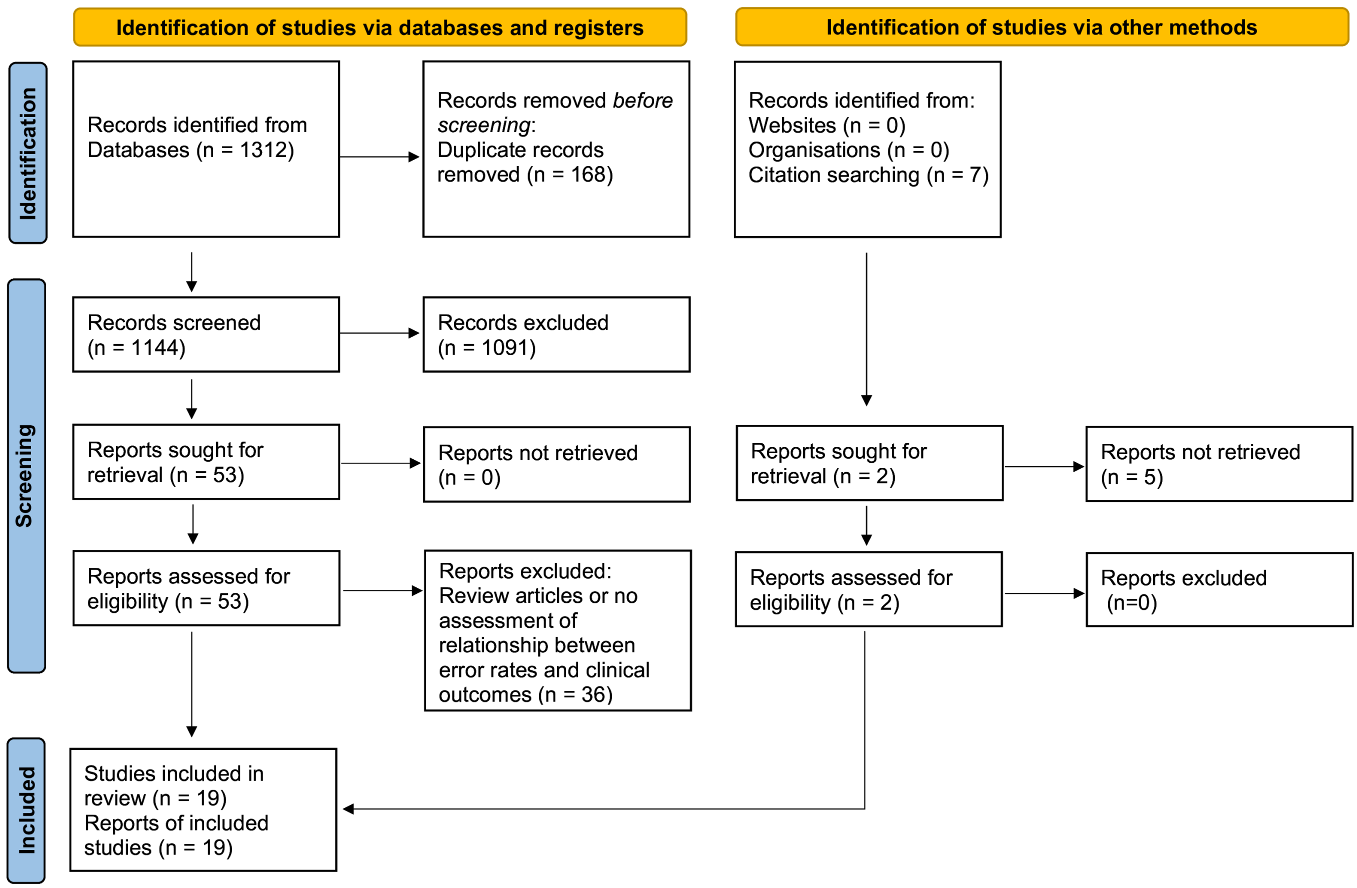

Figure 1 PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

change=145.7 mL; 95% CI: 11.7 to 279.8; p=0.0350).[13] One cross-sectional study showed that patients making no errors had a significantly better mean FEV_1 compared with those making errors (p=0.04)[17] but another showed no correlation[20] (table 1).

Effect of errors on symptoms

A significant improvement in the mean modified Medical Research Council (mMRC) breathlessness scale scores after training in inhaler use with no change in the control group[11] was reported by Göriş *et al* but this was not confirmed other studies.[13 19] Cross-sectional studies have found no significant relationship between mMRC and making errors[5 12 20 25] (table 1) (figure 2).

Effect of errors on health status

Göriş *et al* showed that health status improved after training with no change in the control group[11] but other studies have shown no effect[12 19 21 24] (figure 2).

The PIFotal study found that the errors in ‘breathing in’, ‘holding breath’ and ‘breathing out calmly after inhalation’ using a DPI were significantly associated with poorer Clinical COPD Questionnaire (CCQ) and COPD Assessment Test (CAT) outcomes (respective estimate of the difference (β) in the absolute score and 95% CIs CCQ β 0.16 CI (0.05 to 0.27), CAT β 0.97 CI (0.18 to 1.77); CCQ β 0.14 CI (0.01 to 0.28), CAT β 1.01 CI (0.16 to 2.02); CCQ β 0.27 CI (0.02 to 0.52); CAT β 2.62 CI (0.73 to 4.50)).[28] Other cross-sectional studies show no relationship between errors and health status[12 20 25] (table 1, figure 2).

Effect of errors on exacerbations and healthcare resources utilisation

The study by Cushen *et al*, which used electronic monitoring of adherence and inhalation technique, showed that patients who were adherent but made critical errors experienced more moderate exacerbations (ie, treated with antibiotics or corticosteroids but not hospitalisation) during the 12 months follow-up period than those who were adherent and did not make errors (4.62 (SD 4.69)/person/year vs 4.26 (SD 4.46)) but the difference was not statistically significant.[16] Göriş *et al* reported a significant reduction in moderate exacerbations but no significant difference in severe exacerbations (ie, requiring hospitalisation) after training,[11] but the duration of follow-up was only 3 months, and another study with longer follow-up showed no change in moderate or severe exacerbations[19] (table 1, figure 2).

The initial publication of the PIFotal study reported that none of the errors made using a DPI were significantly associated with moderate or severe exacerbations.[23] However, a subsequent publication claimed that patients with errors in ‘preparation’, ‘hold inhaler

Table 1 Summary of studies reporting relationship between errors using inhaler devices and clinical outcomes

Study	Population	Randomised	Number of patients with COPD	Inhalers	Intervention	Outcomes	Duration of Follow-up	Summary of results	Quality
Prospective Cohort Studies									
Göriș *et al*[11]	C	y	69	p,d	Patients with non-perfect technique randomised to inhaler training or not	Borg MRC SGRQ Exacerbations	3 months	Significant improvement in error rate in intervention group. During follow-up patients in intervention group had significantly fewer 'attacks' (5.9% v 45.7%, p<0.001) and emergency visits (2.9% v 20%, p=0.055), and non-significantly fewer hospitalizations (2.9% v 11.4%, p=0.356). Significant improvement in SGRQ from baseline with intervention (51.9±15.6 to 37.9±14.4, p<0.001) but not in control group (56.9±16.1 to 56.2±15.8, p=0.754). Significant reduction in MRC from baseline with intervention (3.1±0.8 to 2.7±0.9, p<0.023) but not in control group (3.4±0.9 to 3.3 ± − 0.9, p=0.819). No significant change in Borg from baseline with intervention (2.5±1.3 to 2.3±1.3, p=0.307) but significant worsening in control group (2.6±1.3 to 3.3±0.8, p=0.008)	Poor
Maricoto *et al*[13]	M (C)	n	21	u	Inhaler training in all	Error rates mMRC CAT FEV1	6–8 months	FEV1 improved significantly after training in inhaler use (mean change 145.7 mL; 95% CI: 11.7 to 279.8; p=0.0350). No significant change in mean mMRC or CAT (data not reported). No analysis by errors at follow-up	Poor
Cushen *et al*[16]	C	n	226	d	Monitoring of inhaler use with INCA device	Critical error rates Adherence Exacerbations ACM Healthcare use	12 months	Clusters of adherence behaviour were determined based on 90-day mean attempted adherence and mean critical technique error rates. In adherent patients: non-significantly more exacerbations in those with critical errors v good technique 4.62 (SD 4.69)/person/year vs 4.26 (SD 4.46)p>0.05. Higher 12 month mortality in those with critical errors (15%) vs good technique (11%)(No stats presented)	Good
Dabrowska *et al*[19]	M (C)	y	50	u	Patients randomised to inhaler training or not	Error rates CAT SGRQ Exacerbations (Pt report)	3 & 6 months	Not reported separately for asthma and COPD. Reduction in proportion of patients making errors (64% v 40%). In combined population difference in proportion of patients with improvements in symptoms or quality of life or reduction in moderate or severe exacerbations.	Poor
Luley *et al*[21]	C	n	38	p,d,s	Intensive inhaler training for all patients	Error rates CAT	8 days	The median number of handling mistakes per patient decreased at end of intervention (day 8) from 3.0 to 0.5 (p<0.0001). The median CAT Score decreased from 19.5 to 14.5 (p<0.0001) No data on correlation of changes in errors with CAT	Poor
Lindh *et al*[24]	C	n	64	p,d,s	Patients making an error in inhaler technique non-randomsied to additional session of education on inhaler use or not	Error rates CAT	6 months	No differences in the proportions of patients making any errors at follow-up (intervention 50%, control 69%, p=0.130). No difference in mean CAT between baseline and follow-up, either within the intervention group (13.9±5.9 to 14.0±5.8) or within the control group (13.9±6.7 to 14.5±6.8). No data on correlation of change in errors with CAT.	Poor
Dierick *et al*[26]	C	n	12	p	Use of a 'smart' spacer	Error rates FEV1% CCQ	1 month	Mean number of errors per patient per day decreased from 6.40 errors/day to 4.07 errors/ day (paired samples t-test, p=0.038). No significant change in FEV1% (48.2% at baseline, 44.6% at follow-up) No significant change CCQ (2.43 at baseline, 2.67 at follow-up).	Poor

Continued

Table 1 Continued

Study	Population	Randomised	Number of patients with COPD	Inhalers	Intervention	Outcomes	Duration of Follow-up	Summary of results	Quality
Retrospective Case Controlled Studies									
Melani *et al*[5]	M (C)	–	864	p,d	N/A	Proportion of patients making critical errors mMRC ACT and sub-scores Limitations in ADL Frequency of breathlessness Exacerbations Use of rescue medication Disease control Sleep disturbance Unscheduled medical interventions in last 12 months (Pt report)	N/A	Proportion of COPD patients making critical errors not reported separately. 42% of patients had asthma. No association between COPD patients with critical inhaler errors and MRC score (OR 1.10±0.07; p=0.75). Association between ACT score and risk of critical error in COPD patients (OR 1.46 0.18; p<0.005). Overall critical errors associated with increased risk of hospitalisation (p=0.001), emergency room visits (p<0.001), use of antibiotics (p<0.001) and courses of oral corticosteroids (p<0.001). Stated there was also statistical significance (p<0.05) considering COPD patients separately but data not reported	Poor
Maricoto *et al*[12]	M (C)	–	27	p,d	N/A	Proportion of patients making errors CAT mMRC	N/A	78% of COPD patients made one or more errors. Non-significant trend for an association between mMRC and CAT scores and number of errors	Poor
Sriram *et al*[14]	C	–	150*	p,d	N/A	Proportion of patients making errors Adherence Exacerbations (ascertainment not defined)	N/A	Proportion of patients with≥1 error in their inhaler technique was 66% for pMDI, 83% for Turbuhaler, 50% for Handihaler, 75% for Accuhaler. Authors state there was no difference in the frequency of exacerbations between the cohort of patients who did or did not have errors in inhaler technique but data not reported.	Poor
Molimard *et al*[15]	C	–	2935	p,d,s	N/A	Proportion of patients making critical errors Severe exacerbations (ascertainment not defined)	N/A	Critical errors compromising drug delivery were made in 15.4%, 21.2%, 29.3%, 43.8%, 46.9% and 32.1% of inhalation assessment tests with Breezhaler, Diskus, Handihaler, pMDI, Respimat and Turbuhaler respectively. Significant difference in the percentage of patients experiencing severe exacerbations in the previous 3 months: 3.3% (95% CI 2.0 to 4.5) in the absence of critical errors 6.9% (95% CI 5.3 to 8.5) with critical errors (OR 1.86, 95% CI 1.14 to 3.04, p<0.05).	Poor
Gregoriano *et al*[17]	M (C)	–	89	p,d	N/A	Proportion of patients making errors FEV1 CAT SGRQ Exacerbations (Pt report)	N/A	Proportion of asthma & COPD patients with≥1 error in their inhaler technique was 53% for pMDI, 25% for pMDI+spacer, 13% for Discus, 39% for Turbuhaler, 21% for Handihaler, 25% for Breezhaler and 0% for Elipa. Data not reported separately for COPD patients. Patients with no errors had a significantly better mean FEV1 compared with those with errors (p=0.04) (values not given). COPD patients with incorrect device application had a higher CAT score compared with a correct device application (p=0.02) but data not reported. Exacerbation data not reported separately for COPD patients. SGRQ data not reported by error status	Poor

Continued

Table 1 Continued

Study	Population	Randomised	Number of patients with COPD	Inhalers	Intervention	Outcomes	Duration of Follow-up	Summary of results	Quality
Ahn *et al*[18]	C	–	189	p,d,s	N/A	Critical error rates Adherence Exacerbations (MR)	N/A	Patients split in to infrequent (73.5%) and frequent (26.5%) exacerbators. Risk factors for frequent exacerbations were assessed: Any CE was an independent risk factors for frequent exacerbations in multivariate analysis (OR, 2.020; p=0.044)(but not adjusted for adherence). 35.8% of patients with critical errors had frequent exacerbations compared with 19.4% of patients with no critical errors (no statistics reported).	Poor
Duarte-de-Araújo *et al*[20]	C	–	303	p,d,s	N/A	Proportion of patients making critical errors Adherence FEV1% CAT mMRC Exacerbations (ascertainment not defined)	N/A	Critical errors observed in 39.6% of patients. No statistically significant association found between inhaler misuse and CAT score, mMRC grade, FEV1% or exacerbation rates (Data not reported).	Poor
Papaioannou *et al*[22]	M (C)	–	295	p,d,s	N/A	Proportion of patients making errors Exacerbations (MR & Pt report)	N/A	Errors in 45.5% of COPD patients. Mean±SD Exacerbation rates in patients with COPD: incorrect use 1.60±1.21 correct use 0.68±0.71 $p < 0.001$	Poor
Kocks *et al*[23]	C	–	1434 (7005 invited, 1449 agreed)	d	N/A	Proportion of patients making critical errors PIFr Adherence CCQ CAT Exacerbations (MR & Pt report)	N/A	51.7% of patients made one or more critical error. Error 'breathe in' associated with worse CCQ-score after correcting for confounders (0.151 (95% CI 0.037 to 0.265, p=0.023). Trend for 'breathe out' and 'seal inhalation' errors also to be associated with worse CCQ - but not significant. Inhalation errors were not associated with the number of moderate or severe exacerbations. CAT data not reported.	Good
Leving *et al*[27]	C	–	1434	d	N/A	Proportion of patients making errors PIFr HCRU costs	N/A	Overall proportion of patients with≥1 error in their inhaler technique not reported. An error in the inhalation step 'Breathe in' was associated with higher secondary healthcare costs (CR: 2.20, 95% CI(1.37, 3.54), p<0.01) and higher total COPD-related healthcare costs (CR: 1.16, 95% CI(1.03, 1.31), p=0.01) An error in the step 'Hold breath' with higher medication costs (CR: 1.08, 95% CI(1.02, 1.15), p=0.01) and higher total healthcare costs (CR 1.17, 95% CI(1.07, 1.28), p<0.01) An error in the step 'Breathe out calmly after inhalation' with higher medication costs (CR: 1.19, 95% CI(1.04, 1.37), p=0.01). An increase in cumulative errors in all ten inhalation steps was significantly associated with higher total COPDrelated healthcare costs (CR: 1.06, 95% CI(1.02, 1.09), p<0.01) In the adjusted models, no significant associations were observed between the number of inhalation technique errors and specific cost components'	Good

Continued

Table 1 Continued

Study	Population	Randomised	Number of patients with COPD	Inhalers	Intervention	Outcomes	Duration of Follow-up	Summary of results	Quality
Sulku *et al*[25]	C	–	310	p,d,s	N/A	Proportion of patients making critical errors at baseline and at 1 year. CAT mMRC Exacerbations (Pt Report) in 12 months prior to baseline & 12 months prior to FU	N/A	25% made≥1 critical error at baseline and 16% made≥1 critical error at follow-up. No significant association of≥1 critical error with: CAT score or mMRC score or exacerbation rates at baseline or at 1 year.	Poor
Kocks *et al*[28]	C	–	1434	d	N/A	Proportion of patients making errors CCQ CAT Exacerbations (Pt Report)	N/A	Errors in inhalation technique steps 'Breathe in', 'Hold breath', and 'Breathe out calmly after inhalation' significantly associated with poorer CCQ and CAT outcomes (respective estimate of the difference (β) in the absolute score and 95% confidence intervals (CI): CCQ β 0.16 CI(0.05, 0.27), CAT β 0.97 CI(0.18, 1.77); CCQ β 0.14 CI(0.01, 0.28), CAT β 1.01 CI(0.16, 2.02); CCQ β 0.27 CI(0.02, 0.52); CAT β 2.62 CI(0.73, 4.50)). None of the errors made using a DPI were significantly associated with moderate exacerbations. Errors in 'Preparation', 'Hold inhaler in correct position during inhalation' or 'Breathe in' had on average significantly more severe exacerbations (respective rate ratios (RR) and 95% confidence intervals (CI): 2.83, CI(1.30, 6.16); 1.94, CI(1.05, 3.55); 1.85, CI(> 1.00, 3.42)).	Good

*Patients had been admitted to hospital or enrolled on to a pulmonary rehabilitation program.
ACM, all cause mortality; ACT, Asthma control test; Borg, Borg dyspnea scale; C, COPD; CAT, COPD Assessment Test; CCQ, COPD Control Questionnaire; C(M), Mixed but COPD reported separately; d, DPI; FEV1, forced expiratory volume in 1 second; FEV1%, FEV1 as percentage of predicted; INCA, inhaler compliance assessment; n, no; N/A, not applicable; P, prospective; p, pMDI; R, retrospective; s, SMI; u, unspecified; y, yes.

Table 2 The Newcastle-Ottawa Scale assessment of the quality of studies

Study	Selection	Comparability	Outcome	Quality
Prospective cohort studies				
Göriş *et al*[11]	★★★		★★	Poor
Maricoto *et al*[13]	★		★★	Poor
Cushen *et al*[16]	★★★	★	★★	Good
Dabrowska *et al*[19]	★		★★	Poor
Luley *et al*[21]	★		★	Poor
Lindh *et al*[24]	★★		★★	Poor
Dierick *et al*[26]	★★★		★★	Poor
Retrospective case controlled studies				
Melani *et al*[5]	★★★		★★	Poor
Maricoto *et al*[12]	★★★		★★	Poor
Sriram and Percival[14]	★★★		★★	Poor
Molimard *et al*[15]	★★★		★★	Poor
Gregoriano *et al*[17]	★★★		★★	Poor
Ahn *et al*[18]	★★★		★★	Poor
Duarte-de-Araújo *et al*[20]	★★★		★★	Poor
Papaioannou *et al*[22]	★★★		★★	Poor
Kocks *et al*[23]	★★★	★	★★	Good
Sulku *et al*[25]	★★★		★★	Poor
Leving *et al*[27]	★★★	★	★★	Good
Kocks *et al*[28]	★★★	★	★★	Good

in correct position during inhalation' or 'breathe in' had on average significantly more severe exacerbations than patients without these errors (respective rate ratios and 95% CIs: 2.83, 1.30 to 6.16; 1.94, 1.05 to 3.55; 1.85, >1.00 to 3.42).[28] Other cross-sectional studies showed an inconsistent relationship between error rates and moderate or severe exacerbations or healthcare utilisation[5 14 15 18 20 22 25] (table 1, figure 2).

Before adjusting for adherence, Leving *et al*[27] found that errors in the specific inhalation steps 'breathe in' and 'hold breath', as well as the overall total number of errors made, were associated with higher COPD-related healthcare costs. However, when adjusted for adherence, no significant associations were observed between the number of errors and specific cost components.

DISCUSSION

Recommendations by professional organisations, such as GOLD, Canadian Thoracic Society and Spanish Society of Pulmonology and Thoracic Surgery, on the management of COPD, have generally emphasised the need to provide education and training on inhaler device technique to patients and the need to assess a patient's technique before modifying therapy.[29–31] But in some guidelines, this consideration is not discussed,[32] and in practice, it is frequently overlooked.[33] A study of patients in nine countries (Brazil, Canada, France, Germany, Italy, Japan, the Netherlands, the UK and the USA) found that 29% had not had their inhaler technique checked by a healthcare professional within the last 2 years.[34]

Although it seems obvious that patients who do not use a device correctly will not get the full benefit of the drugs they contain, this systematic review found only weak and inconsistent evidence that making fewer mistakes using inhalers is associated with better clinical outcomes, including lung function, symptoms, health status and exacerbation rates in COPD. The prospective cohort studies did not assess changes in clinical outcomes in patients whose error rates were reduced, nor did they account for adherence.[11 13 19 24 26] In the cross-sectional studies, it is impossible to separate cause and effect. For example, patients with poor health status or

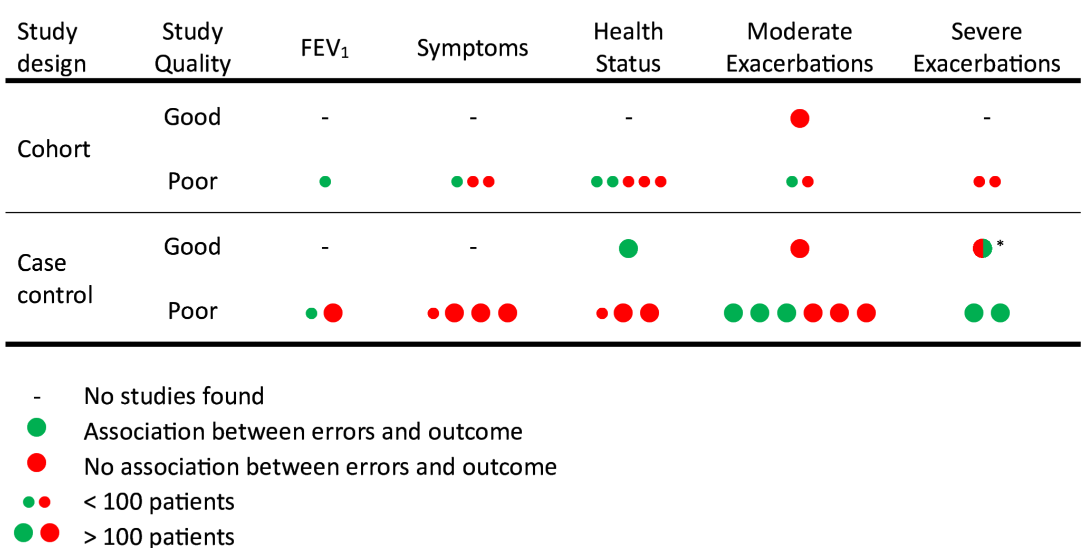

Figure 2 Summary of study results. Each dot represents a study. Moderate exacerbations—requiring antibiotics or corticosteroids but not hospitalisation; severe exacerbations—requiring hospitalisation. *One publication from the PIFotal study reported no significant association but another found an association between three specific errors and more severe exacerbations. FEV_1, forced expiratory volume in 1 s.

lung function may make more errors as they may be more breathless and unable to perform inhalation manoeuvres correctly or poor inhaler technique may have affected the benefits of therapy and led to poor health status and lung function.

Differences in the relative importance of specific errors may also confound the interpretation of the data. Critical errors have largely been defined empirically, on the assumption that they will affect the efficacy of the inhaled therapy. For some, such as failing to remove a protective cap from the inhaler, the assumption seems valid, but the clinical significance of others, such as not sitting or standing straight with head tilted, are more open to question. In some instances, there is evidence which shows that incorrect use impacts the effectiveness of the inhaled therapy. For example, the bioavailability of salbutamol in the lungs is greater after slow inhalation (10 l/min) from a pMDI compared with fast inhalation (50 l/min).[35] In other cases, there is evidence that casts doubt on their importance. For example, studies using the clinical bronchodilator response to inhaled salbutamol as an endpoint found that there was no significant difference in the bronchodilatation induced by a 10s as compared with a 4s or no breath hold.[36 37]

Most studies identified in our systematic review considered errors collectively and only the PIFotal COPD study reported the relationship between specific mistakes using a DPI and outcomes.[23 27 28] The study found that only some errors were related to outcomes but there were inconsistencies. Mistakes in the technique used to breathe in were associated with significantly worse health status, higher secondary healthcare costs and higher total COPD-related healthcare costs.[23 27 28] They were also associated with an increased rate of severe, but not moderate, exacerbations, suggesting that the finding may be confounded and more likely to be due to patients with more severe diseases having problems using inhalers correctly. There was no statistically significant relationship between other errors and worse outcomes.[23 27 28] Of note, failure to 'remove protective cap', was not associated with significantly worse health status or increased exacerbation rates,[28] calling into question the relevance of the overall findings of the study and the definition of critical errors.

One of the main strengths of our review is that it examined the relationship between inhaler technique and outcomes in patients with COPD and did not include patients with asthma. It also included recent studies not considered in previous reviews. There are limitations to the review. The main ones relate to the quality of the studies included. There was heterogeneity in the study designs and short follow-up in most of the prospective cohort studies. Exacerbation rates were mostly based on patient recall and it was not clear how patients were selected for inclusion. Most studies failed to take adherence into account and lacked sufficient detail to enable quantitative synthesis. A narrative review was the only form of synthesis possible, but an individual participant data meta-analysis would have offered the best synthesis had the data been available.

CONCLUSIONS

The lack of evidence found in this narrative review does not mean that teaching patients how to use their inhalers correctly and regularly checking their technique is unimportant. Better prospective studies with longer follow-up examining clinical outcomes in patients who make fewer errors after training are needed. Ideally, such studies should include objective monitoring of inhalation technique and adherence using digital inhalers, as well as examining the effect of specific errors.

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Search Strategies

PubMed

#1 (((((critic*[Text Word])) AND (error*[Text Word]))) AND (inhaler*[Text Word])) AND ((COPD[MeSH Terms]) OR ((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ((("pulmonary"[All Fields] AND "disease"[All Fields]) AND "chronic"[All Fields]) AND "obstructive"[All Fields])) OR "chronic obstructive pulmonary disease"[All Fields]) OR "copd"[All Fields]))

#2 (((exacer*[Text Word]) OR (outcome*[Text Word])) AND (error*[Text Word]) AND (inhaler*[Text Word])) AND ((COPD[MeSH Terms]) OR ((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ((("pulmonary"[All Fields] AND "disease"[All Fields]) AND "chronic"[All Fields]) AND "obstructive"[All Fields])) OR "chronic obstructive pulmonary disease"[All Fields]) OR "copd"[All Fields]))

#3 (((exacer*[Text Word]) OR (statu*[Text Word]) OR (contro*[Text Word])) AND ((error*[Text Word]) OR (mistak*[Text Word])) AND (inhaler*[Text Word])) AND ((COPD[MeSH Terms]) OR ((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ((("pulmonary"[All Fields] AND "disease"[All Fields]) AND "chronic"[All Fields]) AND "obstructive"[All Fields])) OR "chronic obstructive pulmonary disease"[All Fields]) OR "copd"[All Fields]))

#4 #1 OR #2 OR #3

Embase & APA PsycInfo

1 critic*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
2 error*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
3 1 and 2
4 inhaler*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
5 3 and 4
6 COPD.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
7 pulmonary disease, chronic obstructive.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
8 pulmonary.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
9 disease.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
10 8 and 9
11 chronic.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm] 2575565
12 10 and 11
13 obstructive.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
14 12 and 13
15 6 or 7 or 14
16 5 and 15
17 exacer*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
18 outcome*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
19 17 or 18
20 error*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
21 19 and 20

22 21 and 4
23 22 and 15
24 statu*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
25 contro*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
26 24 or 25 or 17
27 mistak*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, tc, id, tm]
28 27 or 20
29 28 and 26
30 29 and 4 and 15
31 16 or 23 or 30

Cochrane
#1 critic*
#2 error*
#3 inhaler*
#4 #1 AND #2 AND #3
#5 (pulmonary) AND (disease) AND (chronic) AND (obstructive):ti,ab,kw (Word variations have been searched)
#6 (chronic obstructive pulmonary disease) (Word variations have been searched)
#7 (copd) (Word variations have been searched)
#8 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
#9 #5 OR #6 OR #7 OR #8
#10 #4 AND #9
#11 exacer*
#12 outcome*
#13 #11 OR #12
#14 error*
#15 #13 AND #14
#16 #3 AND #15
#17 #16 AND #9
#18 statu*
#19 contro*
#20 #18 OR #19 OR #11
#21 mistak*
#22 #21 OR #14
#23 #21 AND #20
#24 #23 AND #3 AND #9
#25 #10 OR #17 OR #24

Google Scholar
"copd" inhale* (exacerbat* OR outcome* OR control) (error* OR mistake*)

ID	Citation	Abstract	DESIGN	Population	Randomised	n with COPD	inhalers	Intervention	Outcomes	Summary of Results	FEV1	mMRC	Borg	SGRQ/CAT/CCQ	Exacs	HCRU
Unique identifier		Abstract from publication	Prospective Retrospective	Mixed COPD & asthma COPD	Yes No	Number of subjects in study	u – unspecified p – pMDI d – DPI s – SMI	Description of study intervention	COPD outcomes measured	Text summary of findings including satistics (if any)	Text summary of findings regarding FEV1 changes including satistics (if any)	Text summary of findings regarding mMRC changes including satistics (if any)	Text summary of findings regarding breathlessness measured using a Borg scale including satistics (if any)	Text summary of findings regarding health status including satistics (if any)	Text summary of findings regarding exacerbation rates including satistics (if any)	Text summary of findings regarding healthcare resource utilization including satistics (if any)

Supplementary Table 1. Data extraction template.