Device use errors with soft mist inhalers: A global systematic literature review and meta-analysis

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Abstract

Inhaled bronchodilators are the cornerstone of treatment for chronic obstructive pulmonary disease (COPD). Soft mist inhalers (SMIs) are devices that deliver bronchodilators. Although correct device use is paramount to successful medication delivery, patient errors are common. This global systematic literature review and meta-analysis examined device use errors with SMIs among patients with obstructive lung diseases. PubMed, EMBASE, PsycINFO, Cochrane, and Google Scholar were searched to identify studies published between 2010 and 2019 that met the following inclusion criteria: (a) English language; (b) a diagnosis of COPD, bronchitis, or emphysema; and (c) reported device use errors among adults receiving long-acting bronchodilator treatment with Respimat® SMI (i.e. Spiriva®, Stiolto®, Spiolto®, and Striverdi®). Descriptive statistics examined sociodemographics, clinical characteristics, and device use errors. Meta-analysis techniques were employed with random-effects models to generate pooled mean effect sizes and 95% confidence intervals (CIs) for overall and step-by-step errors. The I^2 statistic measured heterogeneity. Twelve studies ($n = 1288$ patients) were included in this meta-analysis. Eighty-eight percent of patients had COPD, and most had moderate/very severe airflow limitation (Global Initiative for Chronic Obstructive Lung Disease spirometric stages II to IV). Aggregate results revealed that 58.9% (95% CI: 42.4–75.5; $I^2 = 92.8\%$) of patients made ≥1 device use errors. Among 11 studies with step-by-step data, the most common errors were failure to (1) exhale completely and away from the device (47.8% (95% CI: 33.6–62.0)); (2) hold breath for up to 10 seconds (30.6% (95% CI: 17.5–43.7)); (3) take a slow, deep breath while pressing the dose release button (27.9% (95% CI: 14.5–41.2)); (4) hold the inhaler upright (22.6% (95% CI: 6.2–39.0)); and (5) turn the base toward the arrows until it clicked (17.6% (95% CI: 3.0–32.2)). Device use errors occurred in about 6 of 10 patients who used SMIs. An individualized approach to inhalation device selection and ongoing training and monitoring of device use are important in optimizing bronchodilator treatment.

Keywords

Meta-analysis, COPD, chronic obstructive pulmonary disease, soft mist inhaler, inhaler errors, Respimat®, systematic literature review

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Introduction

Chronic obstructive pulmonary disease (COPD) is among the leading causes of morbidity and mortality worldwide.[1,2] Based on estimates from the Burden of Obstructive Lung Disease study, about 8.9% of the global population is diagnosed with COPD, representing 578 million adults.[3] The annual death toll from COPD is estimated to be 3.2 million globally.[2] Economically, the cost burden associated with COPD varies from <US$680 per patient in countries outside of the United States (US) to >US$6200 per person in the US.[4]

Inhaled bronchodilator therapy remains the cornerstone of pharmacological treatment for COPD. Bronchodilators can be administered through several types of commercially available devices including metered-dose inhalers (MDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and nebulizers.[5] Each device type has advantages and disadvantages. MDIs are portable devices that are fast acting on the airways following one or two puffs taken over a few seconds. They require priming, shaking prior to use, coordination between actuation and inhalation, slow and steady inspiration, and breathholding.[6,7] In addition, since MDIs contain propellants, patients often experience a cold Freon-like effect, an inadvertent reaction to the chilling sensation that reaches the back of the throat following actuation of the device.[8] DPIs are compact portable devices that can be administered in one or two puffs over a few seconds. They were developed to remove the need for propellant-type liquids and to simplify formulations for highly insoluble therapeutic agents. However, DPIs need relatively high inspiratory flow to disaggregate the powder and deliver medication making them less useful for some of the more severely limited COPD patients.[7] DPIs also result in high oropharyngeal deposit, similar to MDIs, and most are moisture sensitive.[8,9] SMIs are portable devices that do not contain propellants and can be used in patients with lower inspiratory flow rates.[9] The spray duration of SMIs is approximately 1.2 seconds which is considerably longer than MDIs.[10] However, as is the case with MDIs, SMIs also require hand–breath coordination and breathholding. Nebulizers produce a fine mist for medication administration for up to 20 minutes and have been used for many years in the treatment of COPD.[6,7] They do not require priming, hand–breath coordination, or breathholding and are able to aerosolize medication that the patient can inhale with regular tidal breathing.[8] There are different types of nebulizers (jet, ultrasonic, and mesh) in the market, and each varies in speed of treatment administration, ease of operation, and portability.[11]

Health-care providers consider several factors in selecting inhalation devices for their patients. Important considerations include inspiratory flow sufficiency, hand–breath coordination, cognitive and mental aptitudes, and the patient's fine motor skills.[6,7,12–14] In addition, patient and caregiver preferences regarding device features and costs can influence selection.[7,15–17]

Regardless of inhalation device types and characteristics, the patient's ability to correctly use the device is paramount to successful treatment.[18,19] Numerous studies have shown that incorrect inhalation device technique can compromise medication delivery, increase the risk of exacerbations, result in higher health resource utilization, and lead to premature mortality.[20–24] To this end, several systematic and narrative literature reviews, with and without a meta-analysis, have been conducted on inhaler errors specific to MDIs, DPIs, or both.[6,7,19,20,24–37] However, similar studies on device use errors with SMIs have not been conducted. To address the existing knowledge gap, this global systematic literature review and meta-analysis was conducted to examine the prevalence and types of device use errors among adult patients with COPD who were receiving long-acting bronchodilator treatment with an SMI.

Methods

Search strategy

The Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[38] were applied to conduct a literature search of articles published between January 1, 2010 and February 1, 2019 across five databases, including PubMed, EMBASE, PsycINFO, Cochrane, and Google Scholar. Selection of published articles was restricted to those that met the following inclusion criteria: (a) English language; (b) a diagnosis of COPD, bronchitis, or emphysema; and (c) reported device use errors among adults receiving long-acting bronchodilator treatment with Respimat® SMI (i.e. Spiriva®, Stiolto®, Spiolto®, and Striverdi®). Iterative combinations of the following keywords were used during the search process: soft mist inhaler, SMI, Respimat, Stiolto Respimat, Spiolto Respimat, Spiriva Respimat, Striverdi Respimat, inhaler error, inhalation technique error, inhaler
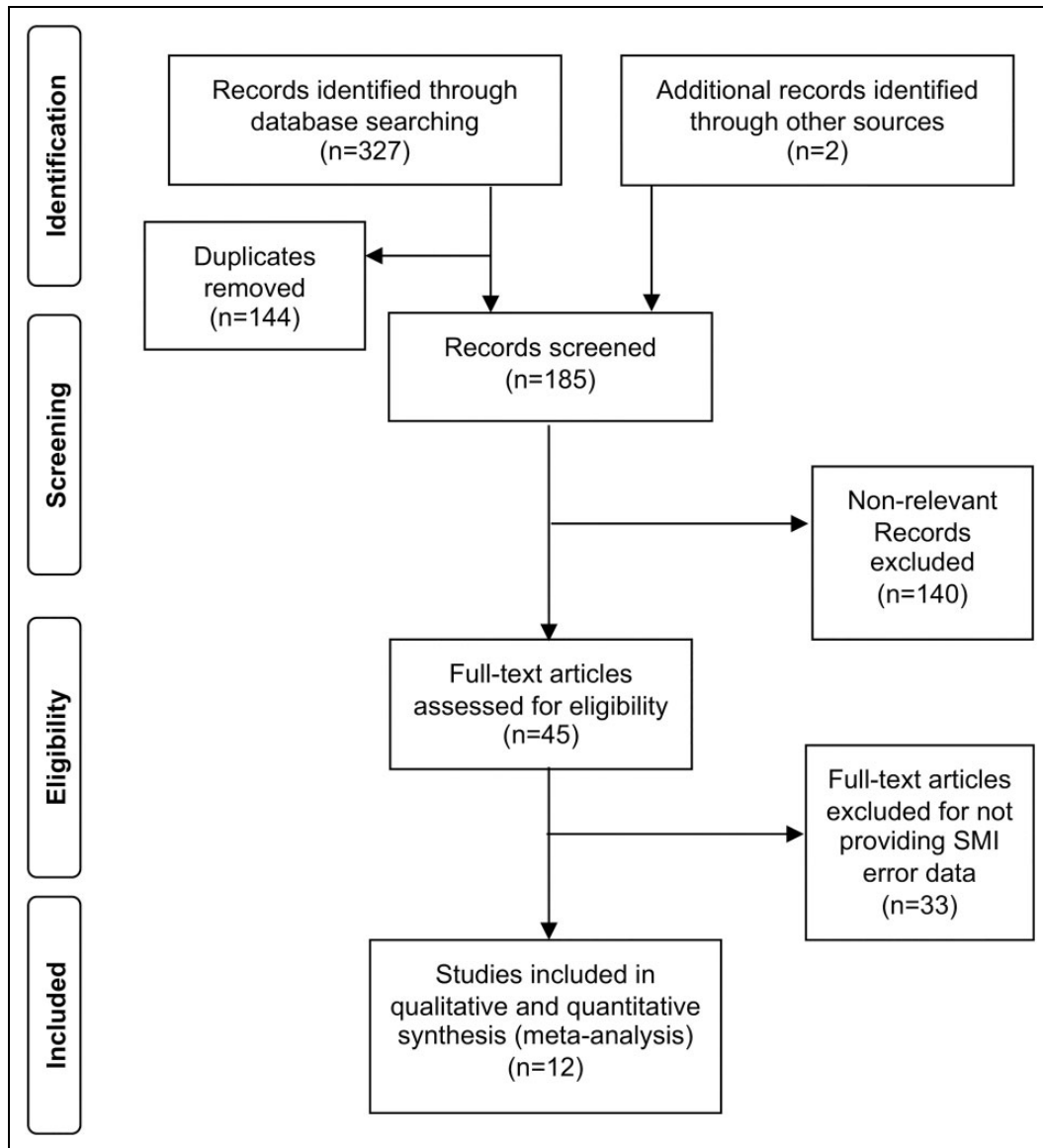
Figure 1. PRISMA flowchart. PRISMA: Preferred Reporting Item for Systematic Reviews and Meta-Analyses; SMI: soft mist inhaler.

mistake, critical errors, improper inhaler technique, inhalation error rate, inhalation failure rate, device handling errors, dose preparation errors, and dose emission errors. To be more comprehensive and balanced in our search strategy, all references within the articles identified from electronic searches were reviewed for relevance which extended the search period from January 1, 2005 to February 1, 2019.

A total of 327 publications met our initial screening criteria (Figure 1). An additional two publications were identified through a manual search. After removing duplicate studies ($n = 144$), 185 abstracts were examined further to assess relevance. By eliminating 140 abstracts that did not meet the eligibility criteria, 45

full-text articles remained and were reviewed in detail. Among these articles, 33 did not provide information on device use errors, resulting in a total of 12 publications that were included in this meta-analysis.[22,39–49] Since this study involved reviewing aggregate level secondary data published in publicly available studies and there was no access to primary patient-level data, protocol approval by the Institutional Review Board and Ethical Committee was waived.

Data extraction and quality assessment

The following data were extracted from each publication based on availability: (a) patients'

sociodemographic characteristics (i.e. age and sex), (b) primary diagnosis, (c) COPD severity (i.e. Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity rating or forced expiratory volume in 1 second (FEV_1), (d) prevalence of overall errors defined as ≥ 1 device use error, and (e) errors made at each inhalation step. Three trained independent reviewers graded the quality of each study. Publications that met the following criteria were classified as having poor quality and excluded from the meta-analysis: (a) combined error rates across multiple devices, (b) reported error rates for fewer than five patients, and (c) did not provide quantifiable data. For randomized controlled trials, quality was assessed using the Cochrane Collaborative criteria.[50] For cross-sectional and observational cohort studies, quality was assessed using applicable scales by Newcastle and Ottawa.[51]

Respimat SMI device use steps

Device use errors were based on the patients' ability to correctly complete the following 14 inhalation steps:[10] (1) checking the cartridge or capsule, (2) holding the inhaler in the upright position, (3) turning the base in the direction of the arrows until it clicks, (4) opening the cap, (5) not activating the inhaler inadvertently, (6) exhaling completely and away from the inhaler, (7) closing lips around the mouthpiece, (8) holding the inhaler in a horizontal position so that it is pointing to the back of throat, (9) pressing the dose-release button while taking a slow and deep inhalation, (10) continuing to inhale slowly and deeply through the mouth, (11) holding breath up to 10 seconds, (12) removing the inhaler from the mouth and breathing out, (13) repeating steps for the second puff, and (14) closing the cap. Dose preparation (priming) steps for first time device use were excluded from the analyses since only two studies[39,40] reported these types of errors. Selected steps (i.e. steps 1, 5, 8, 12, 13, and 14) for which data were provided for fewer than four studies were excluded from the step-by-step error analysis.

Statistical analysis

Descriptive statistics including frequencies, means, medians, standard errors, standard deviations, and proportions for variables of interest were computed and compared across the studies. The prevalence of overall device use errors with SMIs was computed based on the reported proportion of patients who made at least one device use error during the inhalation process. For studies that did not provide an overall error rate,[41–43] it was inferred based on the reported inhalation step with the highest frequency of error. For one study,[44] the overall device use error was considered the same as the reported error rate from the single inhalation step for which data were provided. That study also reported patients using Spiriva without specifying whether the medication was delivered via Respimat or Handihaler®. After contacting the authors, it was presumed that medications were delivered via Respimat. For another study,[45] overall errors were inferred from the mean number of errors per patient. For studies that reported inhalation technique errors before and after an intervention, only baseline (i.e. pre-intervention) error data were used in our analysis.

Step-by-step device use errors were also analyzed across 11 studies that provided this level of data. For studies that presented error data graphically, numeric values were estimated by interpreting graphic representations. The following additional calculations were performed, depending on selected scenarios: (1) for studies that provided results as a percentage of patients who correctly performed each device use step, the results were converted to the percentage of patients who performed each step incorrectly; and (2) for studies that reported two error rates for each device use step, a mean value was computed and used in our analysis.

Meta-analysis

Information specific to the prevalence of overall and step-by-step device use errors was gathered in accordance with the recommendations outlined in Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines for meta-analysis and systematic reviews.[52] Pooled effect estimates (weighted proportions) and 95% confidence intervals (CIs) were computed using the approximation of a binomial distribution. Forest plots were generated to visually examine the degree to which the effect estimates of each study distributed around the pooled effect estimates.[53] The I^2 statistic was used to assess heterogeneity.[54,55] I^2 values of 0–25%, 25–50%, 50–75%, and 75–100% were considered as benchmarks to represent little/negligible, moderate, considerable, and substantial/large degree of heterogeneity, respectively.[54,56] Given the relatively few number of studies and the expectation that there would be between-studies variability, a random effects model was adopted for the meta-analysis.[54,57,58] Sensitivity analysis was performed using the leave-one-out cross-validation

Table 1. Patient and study characteristics.[a]

Study	Study design	Patients (N)	Mean age (±SD/range)	Sex, N (%)	Diagnosis	COPD severity, N (%)
Ding et al.[39]	CS	31 (All SMI users)	59.1[b] (40–76)	M: 14 (45) F: 17 (55)	COPD	GOLD II: 11 (35) GOLD III: 17 (55) GOLD IV: 3 (10)
Ngo et al.[46]	CS	70 (22 SMI users)	68.6 (±8.7)	M: 65 (93) F: 5 (7)	COPD	GOLD I: 3 (4) GOLD II: 6 (9) GOLD III: 8 (11) GOLD IV: 53 (76)
Bournival et al.[47]	CS	67 (All SMI users)	69.8 (±8.3)	M: 36 (54) F: 31 (46)	COPD	GOLD I: 3 (4) GOLD II: 24 (36) GOLD III: 10 (15) GOLD IV: 6 (9) Missing: 24 (36)
Liang et al.[48]	CS	298 (223 SMI users)	72.1 (±9.0)	M: 284 (95) F: 14 (5)	COPD	—
de Oliveira et al.[40]	RCT	140 (135 SMI users)	63.5 (±8.2)	M: 78 (56) F: 62 (44)	COPD	—
Windisch et al.[45]	RCT	152[c] (8 SMI users)	67.4[b]	M: 74 (49) F: 78 (51)	COPD	GOLD I: 2 (1) GOLD II: 32 (21) GOLD III: 59 (39) GOLD IV: 59 (39)
Molimard et al. 2017[22]	Cohort	625 (625 SMI users)	65.9 (±11.5)	M: 394 (63) F: 231(37)	COPD	GOLD I: 126 (20) GOLD II: 374 (60) GOLD III: 99 (16) GOLD IV: 15 (2) Missing: 11 (2)
Ohbayashi et al.[41]	RCT	54 (All SMI users)	74.3 (±10.1)	M: 52 (96) F: 2 (4)	COPD	GOLD I: 10 (19) GOLD II: 25 (46) GOLD III: 12 (22) GOLD IV: 7 (13)
Takaku et al.[49]	Cohort	81 (38 SMI users)	72 (±7)	M: 74 (91) F: 7 (9)	COPD	FEV_1, % predicted = 60.6 ± 23.9[d]
Chorao et al.[42]	CS	301 (18 SMI users)	53 (±17)	M: 120 (40) F: 181 (60)	COPD (107) Asthma (194)	—
Steinberg and Pervanas[44]	CS	129 (38 SMI users)	65.9 (23–93)	M: 61 (47) F: 68 (53)	COPD (76) Asthma (44) Other[e] (9)	—
Asakura et al.[43]	Cohort	29 (All SMI users)	74 (61–85)	M: 29 (100)	COPD	GOLD I: 9 (31) GOLD II: 12 (41) GOLD III: 6 (21) GOLD IV: 2 (7)
Total		1977 (1288 SMI users)		M: 1281 (65) F: 696 (35)	COPD: 1730 (88) Asthma: 238 (12) Other[e]: (9)	GOLD I: 153 (9) GOLD II: 484 (28) GOLD III: 211 (12) GOLD IV: 145 (8) Missing: 737 (43)

SD: standard deviation; COPD: chronic obstructive pulmonary disease; CS: cross-sectional; SMI: soft mist inhaler; M: male; F: female; —: no data; GOLD: Global Initiative for Chronic Obstructive Lung Disease; RCT: randomized controlled trial.
[a]Proportions rounded to the nearest percent.
[b]Weighted mean age calculated based on the proportion of males and females in the study population.
[c]Combined for the control and intervention groups at baseline.
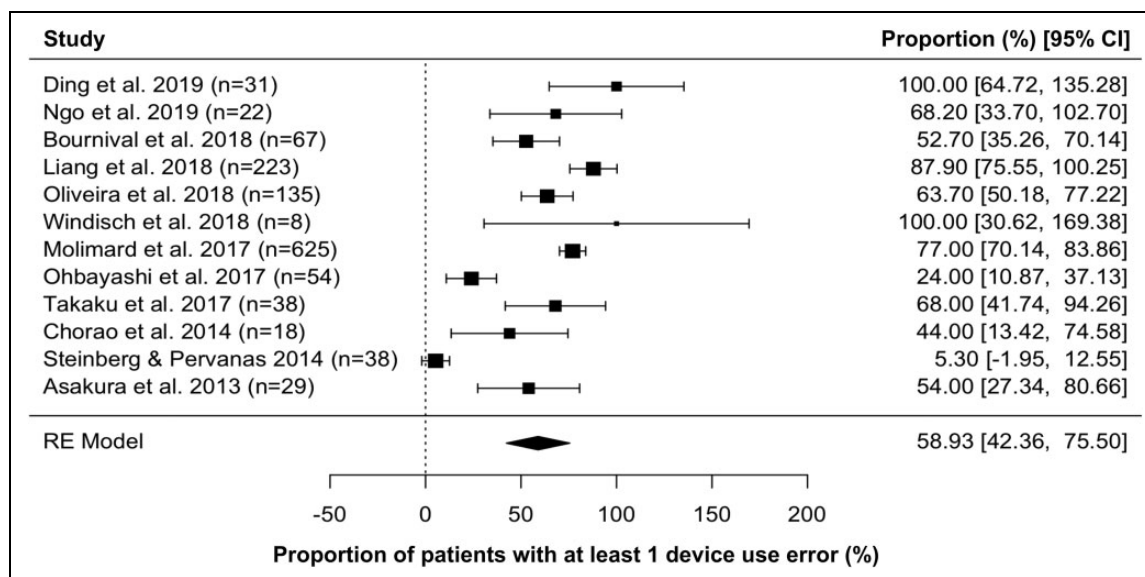[d]Post-brochodilator.
[e]Other, unknown or other illness.

Figure 2. Meta-analysis of device use errors among patients using Respimat® Soft Mist Inhaler™. $I^2 = 92.8\%$; test for heterogeneity: $Q(df = 1) = 273.6$, $p < 0.001$. CI: confidence interval.
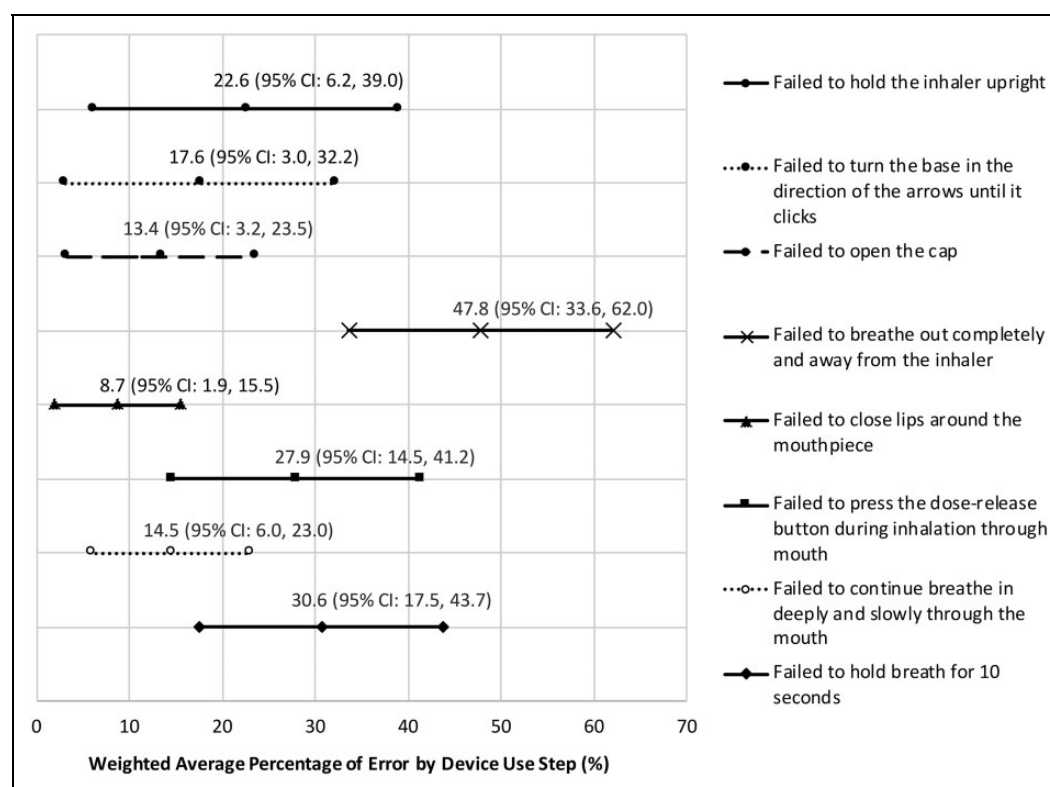

Figure 3. Forest plot showing weighted average percentage of errors by device use step for Respimat® Soft Mist Inhaler™. CI: confidence interval.

technique by removing one study each time to check if an individual study influenced the pooled results.[50,59–62] Funnel plots, Begg and Mazumdar's rank correlation test and Egger's regression test were used to examine potential publication bias, with $p < 0.05$ denoting statistical significance. All meta-analyses were performed using JASP 9.2 software with a restricted maximum likelihood random-effects model.
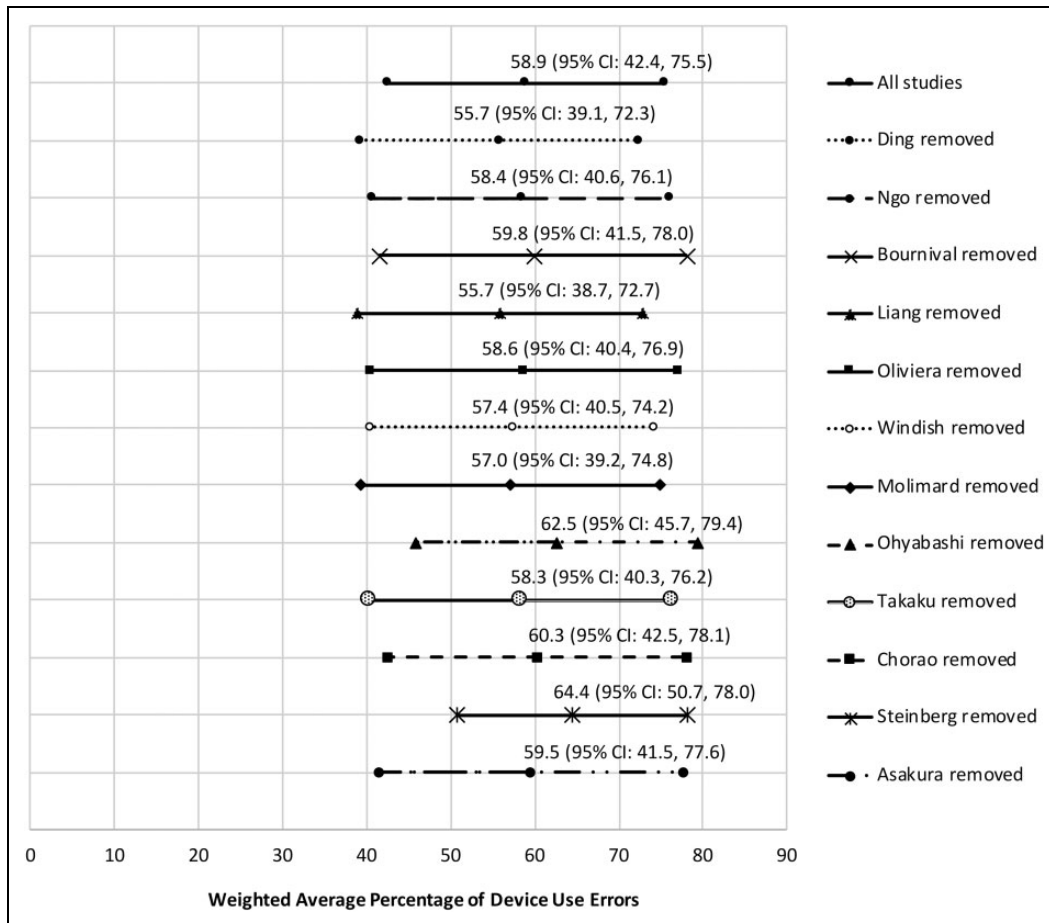
Figure 4. Forest plot showing sensitivity analysis. CI: confidence interval.

Results

Patient characteristics

There were 1977 patients included across the 12 studies, of which 75% were observational studies (50% cross-sectional and 25% cohort studies) and 25% were randomized clinical trials (RCTs; Table 1). Average age ranged from 53 years to 74 years. Nearly twice as many patients were male than female (65% vs. 35%, respectively), and the majority had COPD (88%). Among the studies that reported COPD severity ($n = 993$), 84.6% of all patients were classified as having moderate to very severe COPD (GOLD spirometric stages II to IV). Device use errors with SMIs were provided for a total of 1288 patients.

Overall and step-by-step device use errors with SMIs

The pooled mean effect size across the 12 studies revealed that 58.9% (95% CI: 42.4–75.5) of patients had at least one device use error with their SMIs (Figure 2). Among the 11 studies that reported step-by-step data, the most common errors were failure to (1) exhale completely and away from the device (47.8% (95% CI: 33.6–62.0)); (2) hold breath for up to 10 seconds (30.6% (95% CI: 17.5–43.7)); (3) take a slow and deep breath while pressing the dose release button (27.9% (95% CI: 14.5–41.2)); (4) hold the inhaler upright (22.6% (95% CI: 6.2–39.0)); and (5) turn the base toward the arrows until it clicked (17.6% (95% CI: 3.0–32.2) (Figure 3).

Heterogeneity and sensitivity analysis

Significant heterogeneity was observed across the 12 studies included in our meta-analysis ($I^2 = 92.8\%$; test for heterogeneity: $Q(df = 11)$: 273.6, $p < 0.001$). Sensitivity analysis revealed that the pooled effect size was altered with the removal of five studies[22,39,41,44,49] (Figure 4). The resulting overall effect size was 57.5% (95% CI: 21.2–93.9) across the five studies relative to 59.8% (95% CI: 51.3–68.4) for the remaining seven studies. However, despite the funnel
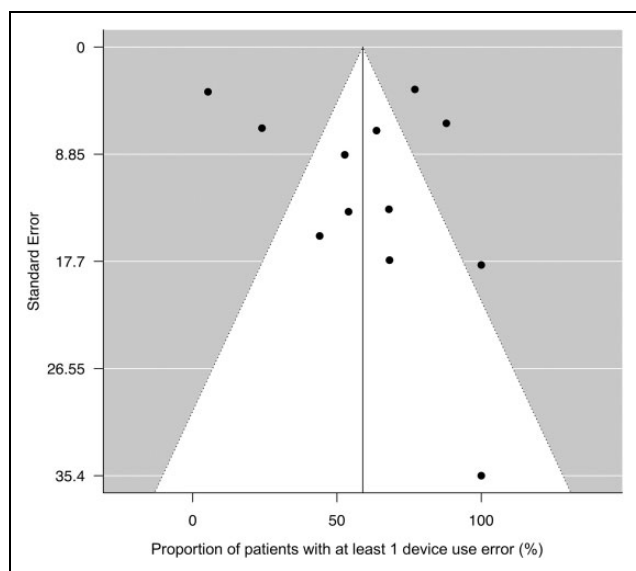
Figure 5. Funnel plot with 95% confidence limits showing publication bias. Five studies outside the funnel include, from left to right, Steinberg and Pervanas[44], Ohbayashi et al.[41], Molimard et al.[22], Liang et al.[48], and Ding et al.[39]. The rest of studies were Ngo et al.[46], Bournival et al.[47], de Oliveira et al.[40], Windisch et al.[45], Takaku et al.[49], Chorao et al.[42], and Asakura et al.[43]. Proportion of patients with at least 1 device use error was not significantly different between the five outlier studies (57.5% (95% CI: 21.2–93.9)) and the rest of studies (59.8% (95% CI: 51.3–68.4)). CI: confidence interval.

plot showing some asymmetry across the studies, the tests assessing potential publication bias were not statistically significant by either Begg and Mazumdar's rank correlation test ($p = 0.500$) or Egger's test ($p = 0.519$) (Figure 5).

Summary of quality assessment

Table 2 provides a summary of the quality assessment scores across the studies. All of the nine observational studies were of good quality. Among the three RCTs, variability in quality was observed, ranging from low to high.

Discussion

In this systematic review and meta-analysis, we found that nearly 6 in 10 COPD patients using SMIs made one or more device use errors. Patients had the most difficulty with inhalation steps that required coordination and breathholding. Overall, about one in two patients did not exhale completely and away from the SMI before inhalation, one in three could not hold their breath as required or had difficulty with hand–

breath coordination, and one in five patients did not hold the SMI in the correct upright position or had difficulty manipulating the base of the device to release the medication.

MDIs and DPIs were the first handheld inhalers used to deliver bronchodilators to COPD patients. Most MDIs require coordination between actuation and inspiration and result in high oropharyngeal deposition. DPIs need a high inspiratory flow and are vulnerable to humidity which adversely affects dosing. Meta-analysis studies of MDIs have shown that device use errors range between 77% and 86.8%.[19,36,37,62] Similarly, a recent meta-analysis of DPIs found inhalation error rates to be as high as 50%.[19] Respimat SMI was developed to overcome the limitations of MDIs and DPIs and to meet the need for a convenient propellant-free inhaler that could effectively deliver aerosols from solutions.[10,15] Our results suggest that device use errors with SMIs are lower than MDIs but higher than DPIs.

COPD patients who are prescribed an SMI typically have suboptimal inspiratory flow and difficulty rapidly coordinating actuation with inhalation.[17,63] Compared to patients using other inhalers, patients using SMIs also tend to be younger, more likely to have severe respiratory disease, and a greater number of comorbidities, particularly neurologic and hypertensive heart diseases.[64] Patients who experience difficulty using an SMI may be candidates for inhalation therapy with other types of devices such as nebulizers. Traditionally, some physicians have had reservations prescribing a nebulizer due to concerns about slower speed of action in medication delivery and inconvenient device portability.[14,65] However, given advances in technology, portable nebulizers with the capability to rapidly administer bronchodilators are now commercially available, thereby giving physicians another alternative for their patients.

Since device satisfaction has been associated with better outcomes,[13,14,40,42,65–67] it seems prudent for clinicians to consider patient preferences during the device selection process. Indeed, GOLD treatment strategies recommend that device selection be based not only on medication availability, costs, and the prescribing physician's preferences, but also on the patient's device preferences and the ability to use the inhalation device.[21]

Regardless of device type, mishandling has been associated with poor health outcomes, more frequent exacerbations, increase in hospitalizations, and higher health resource utilization.[21–23] Thus, the economic

Table 2. Assessment of quality across studies.

Study	Quality score (Newcastle-Ottawa Quality Assessment Scale)[a]		
Ding et al.[39]	Selection ***	Comparability **	Outcome ***
Ngo et al.[46]	Selection ***	Comparability **	Outcome ***
Bournival et al.[47]	Selection ***	Comparability **	Outcome ***
Liang et al.[48]	Selection ***	Comparability **	Outcome ***
Molimard et al.[22]	Selection ****	Comparability **	Outcome ***
Takaku et al.[49]	Selection ***	Comparability **	Outcome ***
Chorao et al.[42]	Selection ***	Comparability **	Outcome ***
Steinberg and Pervanas[44]	Selection ***	Comparability **	Outcome ***
Asakura et al.[43]	Selection ***	Comparability **	Outcome **
	Quality score (GRADE)[b]		
Oliveira et al.[40]	++++ High		
Windisch et al.[45]	++ Low		
Ohbayashi et al.[41]	+++ Moderate		

[a]Scale used to assess quality rating in observational studies; Good quality: three or four stars (*) in selection domain, one or two stars in the comparability domain, and two or three stars in the outcome domain; Fair quality: two stars in the selection domain, one or two stars in the comparability domain, and two or three stars in the outcome domain; Poor quality: zero or one star in the selection domain/zero stars in the comparability domain/zero or one star in the outcome domain.

[b]Scale used to assess quality rating in randomized controlled trials; High: We were confident that the true effect lied close to that of the estimate of the effect; Moderate: We were moderately confident in the effect estimate: The true effect was likely to be close to the estimate of the effect, but there was a possibility that it was substantially different; Low: Our confidence in the effect estimate was rather limited, the true effect may have been substantially different from the estimate of the effect.

consequences of device use errors are considerable in COPD populations.[68–72] Inhaler device errors are considered to be a form of unintentional medication nonadherence.[73,74] Systematic reviews of medication nonadherence (intentional and unintentional) have shown that although adherent COPD patients have higher medication costs than nonadherent COPD patients, total health-care costs of nonadherent patients are substantially higher than adherent patients due to greater inpatient and outpatient costs.[75,76] Given that proper device use has been associated with improving lung function, health status, and quality of life, strategies for reducing device use errors should become a priority for health-care providers, systems, and payers.[21,66]

Our study had several limitations. First, the reasons for device use errors cannot be determined from our analysis. It is possible that patients did not receive adequate training or may have forgotten how to properly use their device. Second, our study is subject to methodological limitations. Potential biases resulting from the subjectivity of the assessor's technique in evaluating patient errors and patient reporting bias (e.g. the Hawthorne effect) may have affected our results. Third, although our study was global in its inclusion of study populations that represented different cultures, the evaluated studies were limited to those published in the English language. Fourth, small sample sizes and incomplete or missing data specific to device use errors with SMIs precluded us from including 34 studies in our analysis. If the inhaler use experiences of the patients included in our analysis were not representative of excluded patients, our findings may not be generalizable to all COPD populations who use SMIs. Lastly, the lack of access to patient-level data in the studies included in our

meta-analysis limited our ability to account for potential confounders and sources of heterogeneity.

Conclusion

Device use errors occurred in almost 60% of patients who were using SMIs. An individualized approach to inhalation device selection, routine monitoring of inhalation technique, and ongoing patient education may help mitigate inhalation errors.[21,77]

Authors' note

An abstract highlighting earlier findings from this article was presented at the CHEST 2019 annual meeting in New Orleans, LA, October 19–23, 2019.

Author contributions

The literature search was conducted by authors MN, SC, and KY; variable selection was performed by MN, SC, CD, and BRC; data extraction was conducted by SC and MN; various phases of study conceptualization, data analysis, and results interpretation were led by MN, SC, CD, and BRC. All authors contributed to the preparation, review, and final approval of the manuscript for publication.

Declaration of conflicting interests

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