CHEST

# Systematic Review of Errors in Inhaler Use
## Has Patient Technique Improved Over Time?

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**BACKGROUND:** Problems with the use of inhalers by patients were noted shortly after the launch of the metered-dose inhaler (MDI) and persist today. We aimed to assess the most common errors in inhaler use over the past 40 years in patients treated with MDIs or dry powder inhalers (DPIs).

**METHODS:** A systematic search for articles reporting direct observation of inhaler technique by trained personnel covered the period from 1975 to 2014. Outcomes were the nature and frequencies of the three most common errors; the percentage of patients demonstrating correct, acceptable, or poor technique; and variations in these outcomes over these 40 years and when partitioned into years 1 to 20 and years 21 to 40. Analyses were conducted in accordance with recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Strengthening the Reporting of Observational Studies in Epidemiology.

**RESULTS:** Data were extracted from 144 articles reporting on a total number of 54,354 subjects performing 59,584 observed tests of technique. The most frequent MDI errors were in coordination (45%; 95% CI, 41%-49%), speed and/or depth of inspiration (44%; 40%-47%), and no postinhalation breath-hold (46%; 42%-49%). Frequent DPI errors were incorrect preparation in 29% (26%-33%), no full expiration before inhalation in 46% (42%-50%), and no postinhalation breath-hold in 37% (33%-40%). The overall prevalence of correct technique was 31% (28%-35%); of acceptable, 41% (36%-47%); and of poor, 31% (27%-36%). There were no significant differences between the first and second 20-year periods of scrutiny.

**CONCLUSIONS:** Incorrect inhaler technique is unacceptably frequent and has not improved over the past 40 years, pointing to an urgent need for new approaches to education and drug delivery.

CHEST 2016; 150(2):394-406

**KEY WORDS:** aerosol therapy; aerosols; inhalation errors; inhalers

**ABBREVIATIONS:** BAMDI = breath-actuated MDI; DPI = dry powder inhaler; MDI = metered-dose inhaler; MDI+IC = MDI with inhalation chamber

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**FUNDING/SUPPORT:** The authors have reported to *CHEST* that no funding was received for this study.

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**DOI:** http://dx.doi.org/10.1016/j.chest.2016.03.041

Current clinical evidence suggests that although contemporary inhaled therapy for asthma has the potential to control disease in most patients,[1,2] control is often not achieved in practice. One prominent reason for poor control is poor inhaler technique, because no matter how good a drug is, it cannot be effective if it does not reach the targeted airways.[3,4]

Problems with technique were recognized shortly after the launch of pressurized metered-dose inhalers (MDIs) in the 1960s,[5] and later reports suggested that the problems persisted despite elaborate initiatives to reduce them.[6-11] Initiatives trying to improve the situation have included regular training programs for patients and health-care professionals; printed instructional material, videos, and software; and measures and devices to make inhalation easier, such as the development of a breath-actuated MDI (BAMDI) and an MDI with inhalation chamber (MDI+IC); and the design of various dry powder inhalers (DPIs) that require an easier inhalation maneuver. A reasonable question that arises, therefore, is to what extent these initiatives have improved problems with inhaler technique over the past 4 decades.

We examined articles published between 1975 and 2014 in which inhaler technique demonstrated by patients with asthma and COPD was assessed by trained observers who classified the errors according to established recommendations and then assessed the overall technique as correct, acceptable, or poor. We also documented the most common errors noted for each inhaler type. Finally, we divided this 40-year period into early and late periods of use and compared the outcome variables to look for time trends.

## Materials and Methods

### *Eligibility, Literature Search, and Selection Process*

Full details of the protocol followed are available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID.CRD42014009347.

Data were extracted from papers assessing the extent and prevalence of incorrect inhaler use in children (minimum age, 5 years) and adults who were receiving inhaled therapy for either asthma or COPD. Articles published in English, French, or Spanish between 1975 and 2014 were evaluated. To be included in the analysis, a study had to meet the following criteria: (1) include an evaluation of inhaler use and technique in its main objective, and (2) contain a description of the assessments made that was based on direct observation of the patients' technique by trained personnel using an inhaler-specific checklist of steps. The recommended maneuvers[12-14] that had to be observed directly and assessed are listed in Table 1. We classified their assessments in rough groupings for analysis. We recorded technique as correct if observers thought all maneuvers were performed in accordance with the recommendations; acceptable (fair or good but suboptimal) if observers thought roughly three-quarters of the maneuvers were as recommended, including all critical aspects; and poor or very poor if fewer than one-half of the maneuvers were correct and/or one or more critical errors were present. The concept of critical error refers to its influence on the generation and lung deposition of aerosol rather than whatever changes it might induce in terms of clinical or therapeutic effects.[15]

Papers providing insufficient information about the maneuvers were excluded. If a study presented data on technique before and after an educational or instructional intervention, we only extracted data prior to the intervention.

MEDLINE (PubMed) was searched using search terms related to inhalers and their use as follows: *inhaler* AND *technique* AND *errors*; *inhaler* AND *education*; *inhaler* AND *technique*; *spacers* AND *asthma*; *metered dose inhaler* AND *utilization* OR *dry powder inhaler* AND *utilization*. We also searched for the brand names of DPIs: Turbuhaler (AstraZeneca), Diskhaler (GalxoSmithKline), Diskus/Accuhaler (GlaxoSmithKline), Rotahaler (GlaxoSmithKline), Novolizer (Meda), Cyclohaler/Aerolizer (Novartis), Handihaler (Boehringer-Ingelheim), Clickhaler (Innovata Biomed), Swinghaler (Otsuka Pharmaceutical), Jethaler (Radiopharm), Benosid N

**TABLE 1** ] Essential Inhalation Maneuver Steps

| |
|---|
| MDI and BAMDI |
| 1. Prepare the device:<br>Both: uncap, shake, hold inhaler (canister vertical, mouthpiece horizontal)<br>BAMDI: raise valve lever |
| 2. Breathe out completely |
| 3. Place teeth and lips around the mouthpiece and fire the device while beginning a slow inhalation |
| 4. Breathe in slowly and deeply, without stopping |
| 5. Hold the breath for 5 to 10 seconds or as long as possible |
| MDI+IC |
| 1. Prepare the device: remove cap, shake the inhaler while holding it vertically with mouthpiece on the bottom, and connect it to the chamber |
| 2. Exhale gently and then place teeth and lips around the chamber's mouthpiece to form a seal |
| 3. Firing and breathing: fire the MDI and take 4 to 5 slow breaths,[a] inhaling from the chamber; hold the last breath for 5 to 10 seconds or as long as possible |
| DPI |
| 1. Prepare the device: uncap, load the inhaler |
| 2. Turn away from the inhaler and breathe out completely |
| 3. Place teeth and lips around the mouthpiece to form a seal |
| 4. Breathe in with one brisk, deep inhalation |
| 5. Hold the breath for 5 to 10 seconds or as long as possible |

The list of steps for the different devices is based on the early descriptions of Newman et al[12] and Dolovich et al[13] and later endorsed by the recommendations of international bodies.[1,2,14] The open mouth technique was also accepted. BAMDI = breath-actuated MDI; DPI = dry powder inhaler; MDI = metered-dose inhaler; MDI+IC = MDI with inhalation chamber.

[a]Tidal breaths (4-5) in small children. A single, long deep expiration outside the chamber and long deep inspiration (small chambers) or several tidal breaths in older children or adults using large chambers were also accepted.

(Farmasan), Easyhaler (Orion Pharma), Elpenhaler (ELPEN), and Nexthaler (Chiesi). The search results were checked against an annotated bibliography available from the National Electronic Library for Medicines.[11] The investigators' own files were also searched. Finally, we checked the reference list in each of the selected articles to identify any studies that might have been missed.

### Outcomes, Data, and Extraction Process

The outcomes of the study were (1) the type and prevalence of the three most frequent errors observed in patients using the various types of inhaler (MDI, BAMDI, MDI+IC, or DPI); (2) the percentage of patients demonstrating correct, acceptable, and poor technique; and (3) changes in these two outcomes over time. For the MDI, BAMDI, and MDI+IC, the first (early) period of use was from 1975 to 1995; the second (late) period was from 1996 to 2014. The first and second periods for the DPI were from 1990 to 2002 and from 2003 to 2014, respectively. Change in the percentage of patients demonstrating correct, acceptable, or poor technique was also assessed by using data for all device types and calculating the averages of 5-year intervals over the 40 years of observations.

The following data were recorded from each selected article: author; year of publication; setting (country); patient type (adult, ≥ 17 years old or child ≥ 5 years old); type of inhaler; number of observed tests of technique for a given inhaler type; percentage of tests with each of the three most frequent errors with each inhaler type; and percentage of technique tests classified as correct, acceptable, or poor. Some of the studies evaluated inhalation technique with more than one device by using the same subjects, whereas other studies tested different subjects' use of the different devices. For simplicity, we will refer to individual tests and the percentages of observed errors made by the tested individuals for each inhaler type.

Recording error reports from heterogeneous studies was complex because some steps (especially step 1, preparation [Table 1]) had various components and these in turn varied with each inhaler type. Furthermore, some of these components were critical, whereas others were less important. When a study reported errors in more than one component in a step, only the frequency of the most important component was tabulated in this review. Some aspects of technique included by some investigators, such as waiting a specified amount of time before the next inhalation or breathing out through the nose, were not taken into account.

In an attempt to enhance recording consistency, a single experienced investigator (J. S.) extracted the data. To reduce the likelihood that this approach might result in errors that might have been detected if two independent investigators extracted and compared data,[16] the same investigator repeated the procedure at a later date, blinded to the results of the previous extraction. A second investigator (I. G.) then independently compared the results of the two sets of data. Disagreements between the two data collections, which were minor and quantitatively did not change the overall results, were nonetheless reassessed.

### Statistical Analysis

Analyses were conducted in accordance with the recommendations of the Cochrane Collaboration (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0)[17], the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology,[18] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[19] Data were recorded in a bespoke spreadsheet and analyzed using StatsDirect (version 2.8.0; http://www.statsdirect.com).

The prevalence—the pooled proportion from a set of weighted proportions—of each error was calculated by means of meta-analysis for each inhaler type. For each variable, the 95% CI was calculated using the approximation of a binomial distribution.[20] To determine the use of a fixed or random effects model, we calculated the $I^2$ index as a measure of heterogeneity.[21] Prevalences were analyzed to ascertain which errors were the most frequent, the relative frequencies of these errors, and the possible change in type and frequency over time. Given the expectation of very great heterogeneity of data (confirmed in all instances by the results of the $I^2$ index, which ranged from 65.3 to 98.1), the random effects model was adopted for all variables.

Funnel plots were drawn, and Egger and Horbold-Egger tests were computed to explore the possibility of publication bias.[22] We also conducted post hoc comparative (sensitivity) analyses of groups with fewer or more than 50 observations of an individual's technique per device-type group.[23]

## Results

Electronic searches yielded 3,695 articles related to inhalation technique. After removal of duplicates and unrelated articles, initial screening led to further exclusions of articles contributing no new data or studies not evaluating overall technique (Fig 1). Articles from the authors' own files and candidates from reference lists were added before the reading of all candidates to check eligibility criteria. This process yielded 144 articles meeting all inclusion criteria.[3,4,24-165] The selected studies were performed in 31 countries; 37 came from North America, 8 from Central or South America, 76 from Europe, 1 from Africa, 4 from the Middle East, 13 from Asia, and 5 from Australia or New Zealand. Fifty-four studies reported data on patients with asthma, 14 on patients with COPD, and the remaining 76 on both types of patients together or on patients with unspecified airway disease. Eighty-one studies provided data on the mean age of their adult subjects (53.6 years). Twenty-five studies reported data on children (age < 18 years); three of these studies also included groups of adults, and 22 enrolled only children. Seventeen of the latter provided data on mean age (9.4 years). The inhalation procedure test protocol checklists were not uniform across studies, but they always included the steps specified in Table 1 and quantified each error as a percentage of the sample.

The 144 selected articles[3,4,24-165] included data on 54,354 subjects and reported a total of 59,584 tests of technique; the number of tests was higher because the subjects in some studies were tested with more than one device. Data were available for 286 groups (ie, subjects tested with a single device) of varying sizes; the mean (SD) number of subjects in each group was 208 (570), with a median of 86 subjects. There were 112 groups,

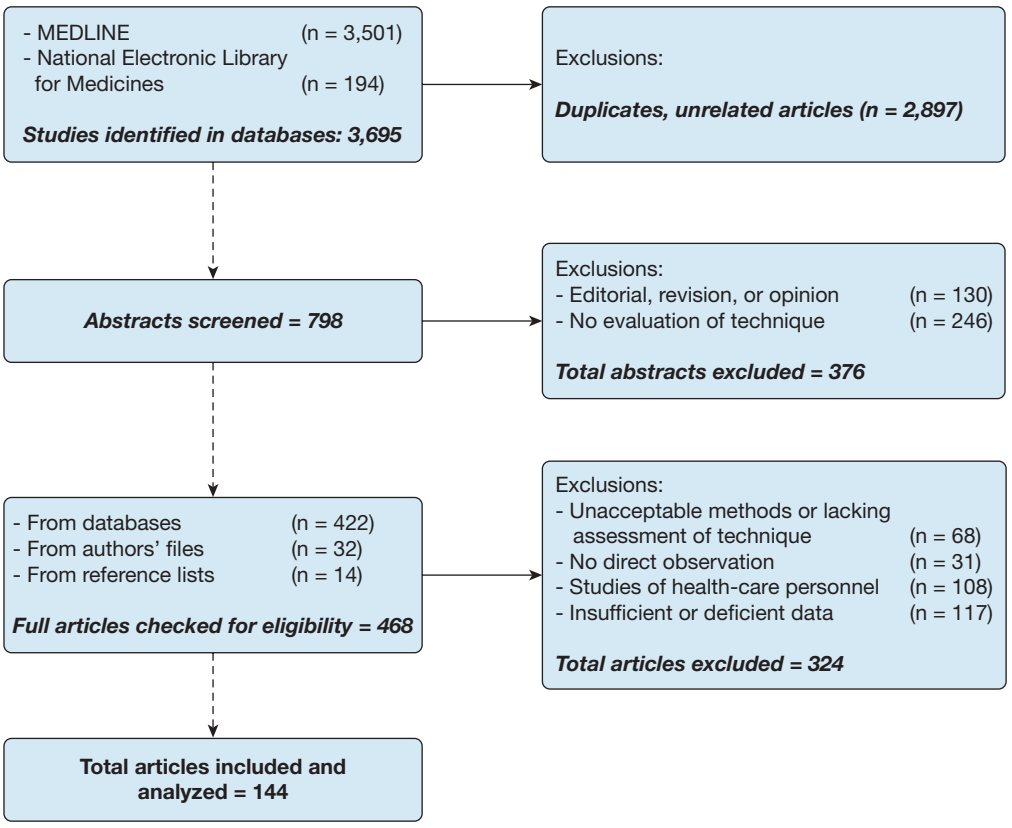


Figure 1 – *Flow diagram of study selection process.*

with 23,720 tests with the MDI; 14 groups included 1,349 tests on children (5.7%). There were 12 groups, with 10,833 tests with the BAMDI; two test groups included 539 children (5.0%). The MDI+IC was tested in 27 groups, with 2,432 tests; 11 of these groups included 1,088 children (44.7%). Of the 130 groups (21,497 tests) tested with the DPI, 15 groups included 1,472 children (6.8%). Thus, children accounted for 7.6% of all subjects tested with one device or another (most often the MDI+IC). The remaining five groups, with 1,100 patients, could not be assigned to a specific device and, therefore, were not included in the analysis of errors. However, their data on correct, acceptable, or poor technique were entered into the overall analysis of the inhalation maneuver.

The times each error appeared as one of most frequent in each article and the estimates of the average frequencies exhibited by all these errors with each type of inhaler are shown in Table 2. We found very minor differences between the results from the early and late periods when we pooled the data for all devices. Given the fact that children amounted to 44.7% of the subjects tested with MDI+IC devices, we analyzed the results of children and adults separately, finding lower error frequencies in children (Table 2). The overall frequency of correct, acceptable, and poor technique can be seen in Table 3. When we looked at these frequencies for the full 40-year period, split into 5-year intervals, we saw no appreciable time trends (Fig 2). The funnel plots showed asymmetry in the data of MDI errors 2 and 4 and DPI errors 1, 2, 4, and 5 (e-Appendix 1). The Egger and Horbold-Egger tests were significant at $P < .05$ for these same errors, indicating the presence of bias.

Relatively small studies (< 50 subjects per group) accounted for 30.8% (88 out of 286) of all the studies. The post hoc sensitivity analysis to explore the influence of small studies showed that their effect on the general results was relatively minor. The small groups generally showed greater variability and slightly higher averages for some of the errors, and the mean percentage of poor technique was similar, at 32% (95% CI, 27%-40%) in the small groups (n = 32) and 30% (95% CI, 27%-36%) in studies with larger groups (n = 75) (Table 4).

Because complete data on all possible errors were not presented in all 144 studies, we undertook a post hoc analysis to test for the possibility that errors expected to be most prevalent might be overestimated because they

**TABLE 2** ] Distribution of the Most Frequent Errors Made With Inhalers

| Inhaler (No. of Tests) | Step | Mean Percentage (95% CI) | Period[a] (No. of Groups) | Mean Percentage (95% CI) |
|---|---|---|---|---|
| MDI (23,720) | Preparation | 30 (24-36) | I (n = 5) | 19 (11-29) |
| | | | II (n = 13) | 34 (27-41) |
| | Full expiration | 48 (43-53) | I (n = 11) | 43 (34-52) |
| | | | II (n = 40) | 49 (43-55) |
| | Coordination | 45 (41-49) | I (n = 35) | 43 (38-49) |
| | | | II (n = 38) | 46 (40-53) |
| | Slow deep breaths | 44 (40-47) | I (n = 21) | 46 (36-56) |
| | | | II (n = 40) | 42 (39-46) |
| | Breath-hold | 46 (42-49) | I (n = 27) | 46 (38-53) |
| | | | II (n = 42) | 45 (41-50) |
| BAMDI (10,833) | Preparation | ID | … | … |
| | Full exhalation | 32 (27-38) | … | … |
| | Breathe in and actuate | ID | … | … |
| | Slow deep breath | 33 (27-39) | … | … |
| | Breath-hold | 39 (35-43) | … | … |
| MDI+IC (2,432) | Prepare, shake, and connect chamber | 33 (25-41) | Child (n = 11) | 31 (23-41) |
| | | | Adult (n = 9) | 34 (20-50) |
| | Exhale and seal chamber outlet with lips | 34 (20-50) | Child (n = 8) | 21 (8-38) |
| | | | Adult (n = 8) | 49 (31-67) |
| | Actuate, 4-5 slow deep breaths, and breath-hold | 38 (30-45) | Child (n = 11) | 31 (23-41) |
| | | | Adult (n = 12) | 44 (33-54) |
| DPI (21,497) | Preparation | 29 (26-33) | I (n = 20) | 25 (19-30) |
| | | | II (n = 49) | 30 (25-35) |
| | Full expiration | 46 (42-50) | I (n = 18) | 52 (46-58) |
| | | | II (n = 58) | 44 (39-49) |
| | Inhale with lips on mouthpiece | 18 (11-25) | I (n = 8) | 18 (11-27) |
| | | | II (n = 1) | ID |
| | Brisk, accelerated deep breath | 22 (19-25) | I (n = 21) | 19 (13-25) |
| | | | II (n = 41) | 23 (19-27) |
| | Breath-hold | 37 (33-40) | I (n = 19) | 37 (27-47) |
| | | | II (n = 50) | 36 (32-40) |

Error frequencies with the MDI, BAMDI, and MDI+IC devices were all ≥ 30%. Errors with the MDI+IC are given for all subjects and both periods together but separately for children and adult subjects. Errors with the MDI alone and the DPI are given by period. DPI errors tended to be somewhat lower than MDI errors in the first period; in the second period, the error frequencies were still higher for the MDI, although the tendency was less clear. ID = insufficient data. See Table 1 legend for expansion of other abbreviations.

[a]MDI: period I, 1975-1995; period II, 1996-2014. DPI: period I, 1990-2002; period II, 2003-2014.

were studied more assiduously. The analyses were repeated ad hoc including only study groups that provided full data on all five steps for two of the devices studied: included were 56 groups for the MDIs (without chambers) and/or BAMDIs (50.0% of the 112 groups) and 52 groups for the DPIs (40.0% of the 130 groups). The results (Table 5) showed that our estimates of the average frequencies for all errors in these subsamples

**TABLE 3** ] Frequency of Correct, Acceptable, and Poor Inhalation Techniques and Their Changes Over Time

| Period | Device | Correct | Acceptable | Poor |
|---|---|---|---|---|
| 1975-2014 | All | 31 (28-35) | 41 (36-47) | 31 (27-36) |
| 1975-1995 | All | 33 (26-40) | 35 (26-45) | 32 (26-37) |
| 1996-2014 | All | 31 (26-36) | 44 (39-59) | 31 (25-37) |
| 1975-2014 | MDI | … | 37 (32-42) | 38 (30-46) |
| 1975-2014 | DPI | … | 44 (34-54) | 23 (18-29) |

Data are presented as mean percentage (95% CI). According to this analysis, one-third of subjects exhibited an inhalation technique that impaired the arrival and/or deposition of aerosol in the lung. Comparison of the 1975-1995 and 1996-2014 intervals shows the stability of the percentage of poor technique and some increase in the numbers of acceptable inhalation technique in the second period. The percentage of poor technique with MDI appears to be clearly higher than that of DPI. See Table 1 legend for expansion of abbreviations.

were somewhat lower than those reported in the sample of groups from all studies (Table 2). Nevertheless, the prevalence of MDI or BAMDI errors 2 to 5 and DPI errors 2 and 5 remained > 30%.

## Discussion

The main finding of this large, systematic review was a high frequency of poor and/or suboptimal inhaler use for all types of devices. The MDI had the highest average frequency of errors (> 40% for steps 2-5). The lower limits of the 95% CIs for errors with this device indicate that even a conservative assessment of the prevalences would be high. The prevalence estimates of DPI errors were somewhat lower, but the preparation, full expiration, and breath-hold maneuvers still had lower limits of the 95% CIs ≥ 25%. Second, we saw no indication that the problem of incorrect or suboptimal use had diminished over the past 40 years, even though considerable effort has been invested in education, training, and device development. The marked diversity in the populations, methodology, types of errors measured, and data presentation of the studies we found dissuaded us from undertaking extensive meta-analyses of the data; however, we believe that the findings of persistently high error rates are robust and clinically important.

The high frequency of incorrect inhaler use and the nature of the most common errors are in agreement with the findings of earlier studies,[3,6,9,10,166] despite our focus on the five most important aspects of technique rather than any or all mistakes, without considering whether they affect the delivery of aerosolized drug to the lung. We had expected that adding holding chambers would reduce MDI errors substantially, but we saw no evidence that this is the case (Table 2). Inhalation chambers differ in shape and volume, and most of


Figure 2 – *The figure shows the average of correct, acceptable, and poor tests over the 40 years of observation. Because not all studies included this information, data were available for 94 groups. Inhaler technique was assessed by the authors of the included articles and considered correct by us when all the steps were performed in agreement with the items listed in Table 1: acceptable when approximately 80% of those steps were correct and no critical error was observed and poor when the researchers observed one or more critical errors and/or there were errors in more than 50% of the inhalation procedure steps. The general impression is one of a stable distribution of averages because there are no major, significant changes in any of the three categories.*

**TABLE 4** ] Error Frequency by Group Size

| Device | Step | Group Size (No. of Groups) | Percentage Error | 95% CI |
|---|---|---|---|---|
| MDI and BAMDI | Coordination | < 50 (n = 24) | 51 | 40-62 |
| | | ≥ 50 (n = 51) | 42 | 38-47 |
| | | All groups (n = 75) | 44 | 41-48 |
| | Slow, deep inspiration | < 50 (n = 20) | 38 | 28-48 |
| | | ≥ 50 (n = 50) | 43 | 39-46 |
| | | All groups (n = 70) | 42 | 39-45 |
| | Breath-hold | < 50 (n = 20) | 46 | 39-53 |
| | | ≥ 50 (n = 61) | 44 | 41-47 |
| | | All groups (n = 81) | 44 | 42-47 |
| MDI+IC | Actuate and slow breaths | < 50 (n = 8) | 31 | 18-46 |
| | | ≥ 50 (n = 15) | 41 | 32-50 |
| | | All groups (n = 23) | 38 | 30-45 |
| DPI | Preparation | < 50 (n = 25) | 40 | 32-50 |
| | | ≥ 50 (n = 46) | 25 | 21-28 |
| | | All groups (n = 71) | 29 | 26-33 |
| | Full expiration | < 50 (n = 24) | 57 | 50-65 |
| | | ≥ 50 (n = 54) | 42 | 37-46 |
| | | All groups (n = 78) | 46 | 42-50 |
| | Breath-hold | < 50 (n = 23) | 49 | 40-58 |
| | | ≥ 50 (n = 47) | 32 | 29-36 |
| | | All groups (n = 70) | 37 | 33-40 |

Data are the estimates of average frequencies of the more frequent errors observed with these types of devices. In general, values were higher in studies with < 50 subjects, in keeping with what is predicted in the literature[22]; however, the slow deep inspiration and breath-hold required for the MDI remained similar. See Table 1 legend for expansion of abbreviations.

**TABLE 5** ] Frequencies of Errors in Studies Reporting Data for All Steps

| Step | Percentage | 95% CI |
|---|---|---|
| MDI and BAMDI (n = 56 groups) | | |
| Preparation | 22 | 18-26 |
| Full expiration | 42 | 38-46 |
| Coordination (inspire and actuate) | 34 | 29-39 |
| Slow deep inspiration | 41 | 37-44 |
| Breath-hold | 41 | 38-45 |
| DPI (n = 52 groups) | | |
| Preparation | 25 | 21-30 |
| Full expiration | 45 | 40-51 |
| Lips on mouthpiece | 8 | 6-11 |
| Brisk, accelerated deep inspiration | 16 | 13-20 |
| Breath-hold | 35 | 31-39 |

The frequencies of errors observed in the selected studies show, in general, percentages somewhat lower than those in Table 2, although they are similar in distribution and still unquestionably high. See Table 1 legend for expansion of abbreviations.

them—but not all—are valved. Chambers are used preferably for small children, the elderly, or physically or mentally disabled adults. These varying circumstances make it difficult to recommend a set of instructions for their use that are as precise as the instructions for the MDI or DPI. In the present study, we resorted to summarizing the proper use of the MDI+IC in three steps (Table 1). In addition, we note that we were able to include relatively few studies for devices with chambers. As a result, no firm conclusions can be drawn about MDI+IC systems at this time, although their use seems to be more problematic for adults, who made errors more often than did children (Table 2). The inclusion of studies with children adds to the heterogeneity of the sum of studies we analyzed. Children represented 7.6% of the subjects overall, but they mainly participated in MDI+IC studies, where they made up 44.7% of the subjects tested.

We also expected DPIs to perform better and were surprised that their error rates were only slightly lower than MDI rates. More than one-third of patients using a

DPI made errors—particularly in dose preparation, expiration, and inspiration—that would reduce drastically the delivery of drug to the lung[15,81] (Table 2). A separate analysis of errors made with the different DPIs that have been developed over the past 30 years would be very helpful, and it also would be instructive to compare the results of such studies with reviews of general, nonspecific data such as the present review. However, our aim was limited to examining the impact of all initiatives to attenuate problems with inhaler technique, which were recognized even in the early years of contemporary inhaled therapy.

The reasons for the high frequencies observed with all inhaler types cannot be inferred from our analysis of the 144 studies we reviewed. Patients may have used their inhaler for long periods since they last received instruction, they may have received little or no instruction, or they may have been instructed in busy clinics and received less attention or follow-up than patients seen in the context of a clinical trial. To our knowledge, changes in the frequencies of incorrect inhaler use over time have not been assessed systematically before this. Our data on the time trend (no improvement) was surprising but seemed to be quite robust. Most authors emphasize the same strategies: careful instruction,[44,60] observation of inhalation technique, and individual matching of inhaler and patient. Training is facilitated by demonstration[44,146] and repeated tuition,[9,81,111] as well as by video instructions, computer assistance, and written material. Our data suggest that either these measures are insufficient or training recommendations generally are not implemented. More research is required not only to address the issues of clinical effectiveness but also to identify new and/or better approaches.

The observed marked diversity in study design, population samples, assessments, and outcomes calls for a widely accepted consensus on how and what to study of this important aspect of real-life use of inhaler therapy in a potentially life-threatening disease. The scarcity of usable information in many articles led to the exclusion of more than 69.2% (324 out of 468) of the candidate articles. The combined problems of diversity and heterogeneity limited our analysis to rough categories. If we do not standardize our methods for studying technique, and cannot measure patients' inhaler use properly, it will continue to be difficult to improve the situation in the future.

## Conclusions

Incorrect inhaler use in patients with asthma and COPD is unacceptably high outside clinical trials and does not seem to have improved over the past 40 years. This may be a major obstacle for achieving good asthma control. New approaches to handling this important problem should be explored. To facilitate comparisons of results, future studies should be based on generally accepted checklists of maneuvers that affect drug delivery. It would be helpful to develop scores that quantify inhaler-specific aspects of technique.

## Acknowledgments

**Author contributions:** J. S. takes the responsibility for (is the guarantor of) the content of the manuscript, including the data and analysis. J. S. states that he initially conceived the work, designed it, and worked out the protocol in detail with the help of I. G. and S. P. He selected the papers to be analyzed, extracted the data from them, and proposed and drafted the interpretation of the results with the help and advice of I. G. and his statistical processing and analysis of the data. Together with I. G. and S. P., he elaborated the global analysis and interpretation of the results and the figures and tables, drafted the submitted article, critically revised its content, and gave his final approval of the version to be published. He is accountable for all aspects of the work in relation to the accuracy and integrity of any part of it. I. G. states that he contributed to the design of this work, revised and corrected the acquired data, decided on and performed its statistical analysis, and participated in the interpretation of the data in the context of the work and the critical revision of its content. He gave his final approval of the version to be published and is accountable for all aspects of the work in relation to the accuracy and integrity of all its parts. S. P. states that he contributed to the conception of the work and the analysis and interpretation of data, participated in the drafting, and was particularly active in the revision and critique of the content in the different drafts of the paper and the identification and outline of its most relevant findings. S. P. participated actively and approved the version to be published and is accountable for all aspects of the work related to the accuracy of any part of it.

**Financial/nonfinancial disclosures:** None declared.

**Other contributions:** We thank Professor Chris Corrigan, PhD, for his suggestions and comments about the manuscript. Mary Ellen Kerans, MA, advised on English language usage in some versions of the manuscript, and we are thankful for her advice.

We also thank members of the Aerosol Drug Management Improvement Team (ADMIT) for the useful comments and stimulating critiques that led to this systematic review. Team members who have not been included as authors are, in alphabetical order, P. J. Barnes, M. Broeders, B. L. Chawes, L. Corbetta, C. J. Corrigan, G. K. Crompton, P. N. R. Dekhuijzen, T. Hausen, F. Lavorini, M. L. Levy, A. Ramalho de Almeida, N. Roche, J. L. Viejo, W. Vincken, and O. S. Usmani.

**Additional information:** The e-Appendix can be found in the Supplemental Materials section of the online article.

## References

1. GINA report, global strategy for asthma management and prevention. Global Initiative for Asthma website. http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed June 26, 2016.
2. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease website. http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/. Accessed June 26, 2016.
3. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J*. 2002;19(2):246-251.
4. Levy ML, Hardwell A, Mcknight E, Holmes J. Asthma patients' inability to use a pressurised metered-dose inhaler (pMDI) correctly correlates with poor asthma control as defined by the Global Initiative for Asthma (GINA) strategy: a retrospective analysis. *Prim Care Respir J*. 2013;22(4):406-411.
5. Saunders KB. Misuse of inhaled bronchodilator agents. *Br Med J*. 1965;1(5441):1037-1038.
6. Paterson I, Crompton G. Use of pressurised aerosols by asthmatic patients. *Br Med J*. 1976;1(6001):76-77.
7. Orehek J, Gayrard P, Grimaud Ch CJ. Patient error in use of bronchodilator metered aerosols. *Br Med J*. 1976;1(6001):76.
8. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest*. 2000;117(2):542.
9. Duerden M, Price D. Training issues in the use of inhalers. *Dis Manage Health Outcomes*. 2001;9(2):75-87.
10. Lavorini F, Magnan A, Dubus JC, et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. *Respir Med*. 2008;102(4):593-604.
11. Burnham T. Inhaler use technique and related interventions: an annotated bibliography. https://use-inhalers.com/sites/default/files/publicationpdf/Reference_Studies_Tom_Burnham.pdf. Accessed June 26, 2016.
12. Newman SP, Pavia D, Clarke SW. How should a pressurised β-adrenergic bronchodilator be inhaled? *Eur J Respir Dis*. 1981;62(1):3-21.
13. Dolovich M, Ruffin R, Roberts R, Newhouse M. Optimal delivery of aerosols from metered dose inhalers. *Chest*. 1981;80(6 suppl):911-915.
14. 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(6):1308-1331.
15. Price D, Bosnic-Anticevich S, Briggs A, et al. Inhaler competence in asthma: common errors, barriers to use and recommended solutions. *Respir Med*. 2013;107(1):37-46.
16. Buscemi N, Hartling L, Vandermeer B, Tjosvold L, Klassen TP. Single data extraction generated more errors than double data extraction in systematic reviews. *J Clin Epidemiol*. 2006;59(7):697-703.
17. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (updated March 2011). http://handbook.cochrane.org/. Accessed April 28, 2016.
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495-1499.
19. Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65-W94.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
21. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. 2003;327(7414):557-560.
22. Egger M, Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J*. 1997;315(7109):629-634.
23. Higgins JPT, Altman DG, Sterne JAC; on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group, eds. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (updated March 2011). http://handbook.cochrane.org/. Accessed April 28, 2016.
24. Epstein SW, Manning CPR, Ashley MJ, Corey PN. Survey of the clinical use of pressurized aerosol inhalers. *Can Med Assoc J*. 1979;120(7):813-816.
25. Gayrard P, Orehek J. Mauvaise utilisation des aerosol-doseurs par les asthmatiques [in French]. *Respiration*. 1980;40(1):47-52.
26. Shim C, Williams MH. The adequacy of inhalation of aerosol from canister nebulizers. *Am J Med*. 1980;69(6):891-894.
27. Crompton GK. Problems patients have using pressurized aerosol inhalers. *Eur J Respir Dis*. 1982;63(suppl 119):101-104.
28. Epstein SW, Parsons JE, Corey PN, Worsley GH, Reilly PA. A comparison of three means of pressurized aerosol inhaler use. *Am Rev Respir Dis*. 1983;128(2):253-255.
29. Lee HS. Proper aerosol inhalation technique for delivery of asthma medicactions. *Clin Pediatr (Phila)*. 1983;22(6):440-443.

30. Frew AJ, Macfarlane JT. Poor inhaler technique may be perpetuated by clinical staff. *Practitioner*. 1984;228(1396):883.
31. Agustí AGN, Ussetti P, Roca J, Montserrat JM, Rodriguez-Roisin R, Agusti-Vidal A. Proper use of metered-dose inhalers [letter]. *Chest*. 1985;88(1):159-160.
32. Becker AB, Simons EE, Benoit TC, Gillespie CA. Terbutaline by metered-dose inhaler: conventional inhaler versus tube spacer for children with asthma. *Ann Allergy*. 1985;55(5):724-728.
33. Pedersen S. Treatment of acute bronchoconstriction in children with use of a tube spacer aerosol and a dry powder inhaler. *Allergy*. 1985;40(4):300-304.
34. Wardman AG, Cooke NJ. Bronchodilator therapy in general practice: what are the problems? *Practitioner*. 1985;229(1405):631-635.
35. Allen SC, Prior A. What determines whether an elderly patient can use a metered dose inhaler correctly? *Br J Dis Chest*. 1986;80(1):45-49.
36. Lahdensuo A, Muittari A. Bronchodilator effects of a fenoterol metered dose inhaler and fenoterol powder in asthmatics with poor inhaler technique. *Eur J Respir Dis*. 1986;68(5):332-335.
37. Pedersen S, Frost L, Arnfred T. Errors in inhalation technique and efficiency of inhaler use in asthmatic children. *Allergy*. 1986;41(2):118-124.
38. Scott-Smith W. Scoring inhaler technique in general practice [letter]. *Practitioner*. 1986;230:96.
39. Armitage JM, Williams SJ. Inhaler technique in the elderly. *Age Ageing*. 1988;17(4):275-278.
40. Horsley MG, Bailie GR. Risk factors for inadequate use of pressurized aerosol inhalers. *J Clin Pharm Ther*. 1988;13(2):139-143.
41. Baciewicz AM, Kyllonen KS. Aerosol inhaler technique in children with asthma. *Am J Hosp Pharm*. 1989;46(12):2510-2511.
42. Borderías L, Hueto J. Inhalation sprays: present status and outlook [in Spanish]. *Med Clin*. 1989;93(17):653-655.
43. Buckley D. Assessment of inhaler technique in general practice. *Ir J Med Sci*. 1989;158(12):297-299.
44. De Blaquiere P, Christensen DB, Carter WB, Martin TR. Use and misuse of metered-dose inhalers by patients with chronic lung disease. *Am Rev Respir Dis*. 1989;140(4):910-916.
45. Manzella BA, Brooks CM, Richards JM Jr, Windsor RA, Soong S, Bailey WC. Assessing the use of metered dose inhalers by adults with asthma. *J Asthma*. 1989;26(4):223-230.
46. Hilton S. An audit of inhaler technique among asthma patients of 34 general practitioners. *Br J Gen Pract*. 1990;40(341):505-506.
47. Hueto J, Borderias L, Eguia VM, et al. Evaluación del uso de los inhaladores: importancia de una correcta instrucción [in Spanish]. *Arch Bronconeumol*. 1990;26(6):235-238.
48. Barritt PW, Staples EB. Measuring success in asthma care: a repeat audit. *Br J Gen Pract*. 1991;41(347):232-236.
49. Brotons B, Franco J, Cabañes M. Evaluation of the use of inhalers [letter] [in Spanish]. *Arch Bronconeumol*. 1991;27(4):190.
50. Diggory P, Bailey R, Vallon A. Effectiveness of inhaled bronchodilator delivery systems for elderly patients. *Age Ageing*. 1991;20(5):379-382.
51. Gibbons B. Metered dose inhaler technique. *Br J Gen Pract*. 1991;41(353):517-518.
52. King D, Earnshaw SM, Delaney JC. Pressurised aerosol inhalers: the cost of misuse. *Br J Clin Pract*. 1991;45(1):48-49.
53. Sprossmann A, Kutschka F, Enk M, Betgmann KC. Factors affecting correct use of metered dose aerosols [in German]. *Z Erkr Atmungsorgane*. 1991;177(1-2):93-95.
54. Dompeling E, van Grunsven PT, van Schayck CP, Folgering H, Molema J, van Weel AC. Treatment with inhaled steroids in asthma and chronic bronchitis: long-term compliance and inhaler technique. *Fam Pract*. 1992;9(2):161-166.
55. Jones KP, Bain DJ, Middleton M, Mullee MA. Correlates of asthma morbidity in primary care. *Br Med J*. 1992;304(6823):361-364.
56. Interiano B, Guntupalli KK. Metered-dose inhalers: do health care providers know what to teach? *Arch Intern Med*. 1993;153(3):81-85.
57. Kumana CR, So SY, Lauder IJ, Ip MS, Lam WK, Kou M. An audit of antiasthmatic drug inhalation technique and understanding. *J Asthma*. 1993;30(4):263-269.
58. Larsen JS, Hahn M, Kochevar JW, et al. Administration errors with a conventional metered dose inhaler versus a novel breath actuated device. *Ann Allergy*. 1993;71(2):103-106.
59. Liam CK, Lo YL, Yap BH, Low SH, Ariwalagam M. Use of pressurised aerosol inhalers among patients attending the Chest Clinic and Primary Care Department of University Hospital, Kuala Lumpur. *Med J Malaysia*. 1993;48(3):273-279.
60. Nimmo CJR, Chen DNM, Martinusen SM, Ustad TL, Ostrow DN. Assessment of patient acceptance and inhalation technique of a pressurized aerosol inhaler and two breath-actuated devices. *Ann Pharmacother*. 1993;27(7-8):922-927.
61. Goodman DE, Israel E, Rosenberg M, Johnston R, Weiss ST, Drazen JM. The influence of age, diagnosis, and gender on proper use of metered-dose inhalers. *Am J Respir Crit Care Med*. 1994;150(5 Pt.1):1256-1261.
62. Kesten S, Elias M, Cartier A, Chapman KR. Patient handling of a multidose dry powder inhalation device for albuterol. *Chest*. 1994;105(4):1077-1081.
63. Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. *J Asthma*. 1994;31(3):193-199.
64. Thompson J, Irvine T, Grathwohl K, Roth B. Misuse of metered-dose inhalers in hospitalized patients. *Chest*. 1994;105(3):715-717.
65. Van der Palen J, Klein JJ, Kerkhof AH. Poor technique in the use of inhalation drugs by patients with chronic bronchitis/pulmonary emphysema [in Dutch]. *Ned Tijdschr Geneeskd*. 1994;138(28):1417-1422.
66. Vichyanond P, Phanichyakarn P, Omar AH, Tam A, Wong E. Ease of handling and efficacy of Bricanyl Turbuhaler in Asian asthmatic children. *Asian Pac J Allergy Immunol*. 1994;12(1):1-6.
67. Connolly MJ. Inhaler technique of elderly patients: comparison of metered-dose inhalers and large volume spacer devices. *Age Ageing*. 1995;24(3):190-192.
68. Jones JS, Holstege CP, Riekse R, White L, Bergquist T. Metered-dose inhalers: do emergency health care providers know what to teach? *Ann Emerg Med*. 1995;26(3):308-311.
69. Liard R, Zureik M, Aubier M, Korobaeff M, Henry C, Neukirch F. Misuse of pressurized metered dose inhalers by asthmatic patients treated in French private practice [in French]. *Rev Epidemiol Sante Publique*. 1995;43(3):242-249.
70. van der Palen J, Klein JJ, Kerkhoff AH, van Herwaarden CL. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease. *Thorax*. 1995;50(11):1183-1187.
71. Benito-Ortiz L, Pérez-Sánchez FC, Nieto-Sánchez MP, Saiz-Monzón ML, Crespo-Fidalgo P, Aldecoa C. Estudio sobre el empleo de broncodilatadores inhalados por los pacientes de atención primaria [in Spanish]. *Aten Primaria*. 1996;18(9):497-501.
72. Boccuti L, Celano M, Geller RJ, Phillips KM. Development of a scale to measure children's metered-dose inhaler and spacer technique. *Ann Allergy Asthma Immunol*. 1996;77(3):217-221.
73. Cragg DK. Efficient inhaler devices. *Br J Gen Pract*. 1996;46(404):199.
74. Gray SL, Williams DM, Pulliam CC, Sirgo MA, Bishop AL, Donohue JF. Characteristics predicting incorrect metered-dose inhaler technique in older subjects. *Arch Intern Med*. 1996;156(9):984-988.

75. Hartert TV, Windom HH, Peebles RS, Freidhoff LR, Togias A. Inadequate outpatient medical therapy for patients with asthma admitted to two urban hospitals. *Am J Med*. 1996;100(4):386-394.

76. Shrestha M, Parupia MFH, Andrews B, et al. Metered-dose inhaler technique of patients in an urban ED: prevalence of incorrect technique and attempt at education. *Am J Emerg Med*. 1996;14(4):380-384.

77. Verver S, Poelman M, Bögels A, Chisholm SL, Dekker FW. Effects of instruction by practice assistants on inhaler technique and respiratory symptoms of patients: a controlled randomized videotaped intervention study. *Fam Pract*. 1996;13(1):35-40.

78. Abley C. Teaching elderly patients how to use inhalers: a study to evaluate an education programme on inhaler technique, for elderly patients. *J Adv Nurs*. 1997;25(4):699-708.

79. Dickinson J, Hutton S, Atkin A, Jones K. Reducing asthma morbidity in the community: the effect of a targeted nurse-run asthma clinic in an English general practice. *Respir Med*. 1997;91(10):634-640.

80. Le Cocguic Y, Zureik M. Evaluation de la manipulation en pratique courante d'un aerosol-doseur declenche par l'inspiration (systeme Autohaler) [in French]. *Rev Pneumol Clin*. 1997;53(1):13-19.

81. Van der Palen J, Klein JJ, Kerkhoff AH, van Herwaarden CL, Seydel ER. Evaluation of the long-term effectiveness of three instruction modes for inhaling medicines. *Patient Educ Couns*. 1997;32(suppl 1):S87-S95.

82. Plaza V, Sanchis J; and the CESEA Group. Medical personnel and patient skill in the use of metered dose inhalers: a multicentric study. *Respiration*. 1998;65(3):195-198.

83. van Beerendonk I, Mesters I, Mudde AN, Tan TD. Assessment of the inhalation technique in outpatients with asthma or chronic obstructive pulmonary disease using a metered-dose inhaler or dry powder device. *J Asthma*. 1998;35(3):273-279.

84. van der Palen J, Klein JJ, Schildkamp AM. Comparison of a new multidose powder inhaler (Diskus/Accuhaler) and the Turbuhaler regarding preference and ease of use. *J Asthma*. 1998;35(2):147-152.

85. De Boeck K, Alifier M, Warnier G. Is the correct use of a dry powder inhaler (Turbohaler) age dependent? *J Allergy Clin Immunol*. 1999;103(5 pt 1):763-767.

86. Tan NC, Ng CJ, Goh S, Lee CE. Assessment of metered dose inhaler technique in family health service patients in Singapore. *Singapore Med J*. 1999;40(7):465-467.

87. van Der Palen J, Klein JJ, van Herwaarden CL, Zielhuis GA, Seydel ER. Multiple inhalers confuse asthma patients. *Eur Respir J*. 1999;14(5):1034-1037.

88. Zureik M, Delacourt C. Evaluation de la facilité d'apprentissage d'un système d'inhalation déclenché per l'inspiration chez l'enfant asthmatique [in French]. *Arch Pediatr*. 1999;6(11):1172-1178.

89. Carrión-Valero F, Maya M, Fontana I, Díaz J, Marín J, Soong S. Inhalation technique in patients with chronic respiratory diseases [in Spanish]. *Arch Bronconeumol*. 2000;36(5):236-240.

90. Chafin C, Tolley E, George C, et al. Gender differences in metered-dose inhaler-spacer device technique. *Pharmacotherapy*. 2000;20(11):1324-1327.

91. Johnson DC, Robart P. Inhaler technique of outpatients in the home. *Respir Care*. 2000;45(10):1182-1187.

92. Kamps AWA, van Ewijk B, Roorda RJ, Brand PL. Poor inhalation technique, even after inhalation instructions, in children with asthma. *Pediatr Pulmonol*. 2000;29(10):39-42.

93. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices. *Respir Med*. 2000;94(5):496-500.

94. Liam CK, Lim KH, Wong CM. Acceptance of the Accuhaler, a multi-dose powder inhaler, among asthmatic patients: a comparison with the pressurized metered-dose inhaler. *Asian Pac J Allergy Immunol*. 2000;18(3):135-140.

95. Alshehri MA. Assessment of inhalation technique in children with asthma, Abha, Saudi Arabia. *J Egypt Public Health Assoc*. 2001;76(1-2):37-51.

96. Diggory P, Fernandez C, Humphrey A, Jones V, Murphy M. Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial. *Br Med J*. 2001;322(7286):1-4.

97. Dow L, Fowler L, Lamb H. Elderly people's technique in using dry powder inhalers [letter]. *Br Med J*. 2001;323(7303):49-50.

98. Epstein S, Maidenberg A, Hallett D, Khan K, Chapman KR. Patient handling of a dry-powder inhaler in clinical practice. *Chest*. 2001;120(5):1480-1484.

99. Hernan-Sotomayor L, Vera A, Naveas G, Sotomayor C. Assessment of techniques and errors in the use of metered dose inhalers in adults [in Spanish]. *Rev Med Chil*. 2001;129(4):413-420.

100. Hesselink AE, Penninx BWJH, Wijnhoven HAH, Kriegsman DMW, van Eijk JTM. Determinants of an incorrect inhalation technique in patients with asthma or COPD. *Scand J Prim Health Care*. 2001;19(4):255-260.

101. Pinto Pereira L, Clement Y, Simeon D. Educational intervention for correct pressurised metered dose inhaler technique in Trinidadian patients with asthma. *Patient Educ Couns*. 2001;42(1):91-97.

102. Caballero-Fontseca F, Sánchez-Borges M, Ben-Joseph R. Prescription patterns and inhalation techniques in a population of persistent asthmatics [abstract]. *J Allergy Clin Immunol*. 2002;109(1 suppl 1):S242.

103. Kamps AWA, Brand PLP, Roorda RJ. Determinants of correct inhalation technique in children attending a hospital-based asthma clinic. *Acta Paediatr*. 2002;91(2):159-163.

104. Pinto Pereira LM, Clement Y, Da Silva CK, McIntosh D, Simeon DT. Understanding and use of inhaler medication by asthmatics in specialty care in Trinidad. *Chest*. 2002;121(6):1833-1840.

105. Scarfone RJ, Capraro GA, Zorc JJ, Zhao H. Demonstrated use of metered-dose inhalers and peak flow meters by children and adolescents with acute asthma exacerbations. *Arch Pediatr Adolesc Med*. 2002;156(4):378-383.

106. Serra-Batlles J, Plaza V, Badiola C, Morejón E; and the Inhalation Devices Sudy Group. Patient perception and acceptability of multidose dry powder inhalers: a randomized crossover comparison of Diskus/Accuhaler with Turbuhaler. *J Aerosol Med*. 2002;15(1):59-64.

107. Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. *Age Ageing*. 2003;32(3):299-302.

108. Botting C, Sutherland M, Wells E, Town I, Sainsbury R, Toop L. The use of inhaled and related respiratory medications in Christchurch rest homes. *N Z Med J*. 2003;116(1187):1-8.

109. Girodet PO, Raherison C, Abouelfath A, et al. Real-life use of inhaler devices for chronic obstructive pulmonary disease in primary care [in French]. *Therapie*. 2003;58(6):499-504.

110. Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of the handling of inhaler devices in real life: an observational study in 3811 patients in primary care. *J Aerosol Med*. 2003;16(3):249-254.

111. Savage I, Goodyer L. Providing information on metered dose inhaler technique: is multimedia as effective as print? *Fam Pract*. 2003;20(5):552-557.

112. Ho SF, O'Mahony MS, Steward JA, Breay P, Burr ML. Inhaler technique in older people in the community. *Age Ageing*. 2004;33(2):185-188.

113. Loh LC, Teng CL, Teh PN, Koh CN, Vijayasingham P, Thayaparan T. Metered-dose inhaler technique in asthmatic patients: a revisit of the Malaysian scene. *Med J Malaysia*. 2004;59(3):335-341.

114. Melani AS, Zanchetta D, Barbato N, et al. Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. *Ann Allergy Asthma Immunol*. 2004;93(5):439-446.

115. Richards JR, Luskin MJ, Krivoshto IN, Derlet RW. Improving metered dose

inhaler technique in the emergency department: a prospective study. *Cal J Emerg Med*. 2004;5(2):27-33.

116. Basheti IA, Reddel HK, Armour CL, Bosnic-Anticevich SZ. Counseling about turbuhaler technique: needs assessment and effective strategies for community pharmacists. *Respir Care*. 2005;50(5):617-623.
117. Burkhart PV, Rayens MK, Bowman RK. An evaluation of children's metered-dose inhaler technique for asthma medications. *Nurs Clin North Am*. 2005;40(1):167-182.
118. Rönmark E, Jögi R, Lindqvist A, et al. Correct use of three powder inhalers: comparison between Diskus, Turbuhaler, and Easyhaler. *J Asthma*. 2005;42(3):173-178.
119. Song WS, Mullon J, Regan NA, Roth BJ. Instruction of hospitalized patients by respiratory therapists on metered-dose inhaler use leads to decrease in patient errors. *Respir Care*. 2005;50(8):1040-1045.
120. Goodyer L, Savage I, Dikmen Z. Inhaler technique in Turkish people with poor English: a case of information discrimination? *Pharm World Sci*. 2006;28(2):107-114.
121. Haro Estarriol M, Castañer CL, Marín-Barnuevo C, Martínez MJA, Perta MDM. Usefulness of teaching how to manage the pressurized canister and the Turbuhaler system in hospitalized patients [in Spanish]. *Arch Bronconeumol*. 2002;38(7):306-310.
122. Luk H, Chan P, Lam F, et al. Teaching chronic obstructive airway disease patients using a metered-dose inhaler. *Chin Med J (Engl)*. 2006;119(19):1669-1672.
123. Sestini P, Cappiello V, Aliani M, et al. Prescription bias and factors associated with improper use of inhalers. *J Aerosol Med*. 2006;19(2):127-136.
124. Walia M, Paul L, Satyavani A, Lodha R, Kalaivani M, Kabra SK. Assessment of inhalation technique and determinants of incorrect performance among children with asthma. *Pediatr Pulmonol*. 2006;41(11):1082-1087.
125. Malot L, Molimard M, Abouelfatah A, et al. Assessment of the handling of inhaler devices in real life: an observational study of children in primary care [in French]. *Arch Pediatr*. 2007;14(10):1190-1195.
126. van Der Palen J, Eijsvogel MM, Kuipers BF, Schipper M, Vermue NA. Comparison of the Diskus inhaler and the Handihaler regarding preference and ease of use. *J Aerosol Med*. 2007;20(1):38-44.
127. Hagmolen of ten Have W, van de Berg NJ, Bindels PJ, van Aalderen WM, van der Palen J. Assessment of inhalation technique in children in general practice: increased risk of incorrect performance with new device. *J Asthma*. 2008;45(1):67-71.
128. Khassawneh BY, Al-Ali MK, Alzoubi KH, et al. Handling of inhaler devices in actual pulmonary practice: metered-dose inhaler versus dry powder inhalers. *Respir Care*. 2008;53(3):324-328.
129. Costa Mdo R, Oliveira MA, Santoro IL, Juliano Y, Pinto JR, Fernandes AL. Educational camp for children with asthma. *J Bras Pneumol*. 2008;34(4):191-195.
130. Schulte M, Osseiran K, Betz R, et al. Handling of and preferences for available dry powder inhaler systems by patients with asthma and COPD. *J Aerosol Med Pulm Drug Deliv*. 2008;21(4):321-328.
131. Wieshammer S, Dreyhaupt J. Dry powder inhalers: which factors determine the frequency of handling errors? *Respiration*. 2008;75(1):18-25.
132. Deerojanawong J, na Sakolnakorn P V, Prapphal N, Hanrutakorn C, Sritippayawan S. Evaluation of metered-dose inhaler administration technique among asthmatic children and their caregivers in Thailand. *Asian Pac J Allergy Immunol*. 2009;27(2-3):87-93.
133. Souza MLM, Meneghini AC, Ferraz É, Vianna EO, Borges M. Knowledge of and technique for using inhalation devices among asthma patients and COPD patients. *J Bras Pneumol*. 2009;35(9):824-831.
134. Toumas M, Basheti IS, Bosnic-Anticevich SZ. Comparison of small-group training with self-directed internet-based training in inhaler techniques. *Am J Pharm Educ*. 2009;73(5):1-7.
135. Bosnic-Anticevich SZ, Sinha H, So S, Reddel HK. Metered-dose inhaler technique: the effect of two educational interventions delivered in community pharmacy over time. *J Asthma*. 2010;47(3):251-256.
136. Rootmensen GN, van Keimpema ARJ, Jansen HM, de Haan RJ. 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(5):1-6.
137. Baqai HZ, Saleem MA, Abair-ul-haq M. Assessment of metered dose inhaler technique in patients with chronic lung disease at government hospitals of Rawalpindi. *J Ayub Med Coll Abbottabad*. 2011;23(1):37-39.
138. Chapman KR, Fogarty CM, Peckitt C, et al. Delivery characteristics and patients' handling of two single-dose dry-powder inhalers used in COPD. *Int J Chron Obstruct Pulmon Dis*. 2011;6(1):353-363.
139. Coehlo ACC, Souza-Machado A, Leite M, et al. Use of inhaler devices and asthma control in severe asthma patients at a referral center in the city of Salvador, Brazil. *J Bras Pneumol*. 2011;37(6):720-728.
140. Giraud V, Allaert FA, Roche N. Inhaler technique and asthma: feasability and acceptability of training by pharmacists. *Respir Med*. 2011;105(12):1815-1822.
141. Giraud V, Allaert FA, Magnan A. A prospective observational study of patient training in use of the Autohaler® inhaler device: the Sirocco Study. *Eur Rev Med Pharmacol Sci*. 2011;15(5):563-570.
142. Hämmerlein A, Müller U, Schulz M. Pharmacist-led intervention study to improve inhalation technique in asthma and COPD patients. *J Eval Clin Pract*. 2011;17(1):61-70.
143. Lee SM, Chang YS, Kim CW, et al. Skills in handling turbuhaler, diskus, and pressurized metered-dose inhaler in Korean asthmatic patients. *Allergy Asthma Immunol Res*. 2011;3(1):46-52.
144. Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med*. 2011;105(6):930-938.
145. Nelson P, Young HN, Knobloch MJ, Griesbach SA. Telephonic monitoring and optimization of inhaler technique. *Telemed J E Health*. 2011;17(9):734-740.
146. Press VG, Arora VM, Shah LM, et al. Misuse of respiratory inhalers in hospitalized patients with asthma or COPD. *J Gen Intern Med*. 2011;26(6):635-642.
147. Roy A, Battle K, Lurslurchachai L, Halm EA, Wisnivesky JP. Inhaler device, administration technique, and adherence to inhaled corticosteroids in patients with asthma. *Prim Care Respir J*. 2011;20(2):148-154.
148. Sleath B, Ayala GX, Gillette C, et al. Provider demonstration and assessment of child device technique during pediatric asthma visits. *Pediatrics*. 2011;127(4):642-648.
149. Batterink J, Dahri K, Aulakh A, Rempel C. Evaluation of the use of inhaled medications by hospital inpatients with chronic obstructive pulmonary disease. *Can J Hosp Pharm*. 2012;65(2):111-118.
150. Chang YS, Park MJ, Bai C, et al. Comparative study of patients in correct usage of and preference for the Swinghaler and Turbuhaler multidose inhalers. *J Asthma*. 2012;49(7):750-756.
151. García-Cárdenas V, Sabater-Hernández D, García-Corpas JP, Faus MJ, Martínez-Martínez F, Benrimoj SI. Errors in Turbuhaler technique in a Spanish population of asthmatic patients. *Respir Care*. 2012;57(5):817-818.
152. Kiser K, Jonas D, Warner Z, Scanlon K, Shilliday BB, DeWalt DA. A randomized controlled trial of a literacy-sensitive self-management intervention for chronic obstructive pulmonary disease patients. *J Gen Intern Med*. 2012;27(2):190-195.
153. Nair S, AnithaKumari K, Fathahudeen A, et al. Technical errors in usage of inhalers among adult patients with obstructive airway disease presenting to a tertiary care center in Trivandrum, Kerala. *Pulmon*. 2012;14(2):52-58.
154. Öztürk C, Kaya A, Bilgin C, et al. Evaluation of inhaler technique and

patient satisfaction with fixed-combination budesonide/formoterol dry-powder inhaler in chronic obstructive pulmonary disease (COPD): data on real-life clinical practice in Turkey. *Tuberk Toraks*. 2012;60(4):301-313.

155. Sleath B, Carpenter DM, Ayala GX, et al. Communication during pediatric asthma visits and child asthma medication device technique 1 month later. *J Asthma*. 2012;49(9):918-925.

156. Bryant L, Bang C, Chew C, Baik SH, Wiseman D. Adequacy of inhaler technique used by people with asthma or chronic obstructive pulmonary disease. *J Prim Health Care*. 2013;5(3):191-198.

157. García-Falcón D, Lawrence KK, Prendes-Columbié MC. Uso inadecuado de la vía inhalatoria en pacientes asmáticos que utilizan salbutamol [in Spanish]. *Rev Peru Med Exp Salud Publica*. 2013;30(2):349-350.

158. Vargas O, Martinez J, Ibanez M, Pena C, Santamaria M. The use of metered-dose inhalers in hospital environments. *J Aerosol Med Pulm Drug Deliv*. 2013;26(5):287-296.

159. Dalcin PTR, Grutcki DM, Laporte PP, Borges de Lima P, Menegotto SM, Pereira RP. Factors related to the incorrect use of inhalers by asthma patients. *J Bras Pneumol*. 2014;40(1):13-20.

160. Harnett CM, Hunt EB, Bowen BR, et al. A study to assess inhaler technique and its potential impact on asthma control in patients attending an asthma clinic. *J Asthma*. 2014;51(4):440-445.

161. Li H, Chen Y, Zhang Z, Dong X, Zhang G, Zhang H. Handling of Diskus dry powder inhaler in Chinese chronic obstructive pulmonary disease patients. *J Aerosol Med Pulm Drug Deliv*. 2014;27(3):219-227.

162. Oliveira PD, Menezes A, Bertoldi A, Wehrmeister F, Macedo S. Assessment of inhaler techniques employed by patients with respiratory diseases in southern Brazil: a population-based study. *J Bras Pneumol*. 2014;40(5):513-520.

163. Onyedum C, Desalu O, Nwosu N, Chukwuka C, Ukwaja K, Ezeudo C. Evaluation of inhaler technique among asthma patients seen in Nigeria: an observational cross sectional study. *Ann Med Health Sci Res*. 2014;4(1):67-73.

164. Voshaar T, Spinola M, Linnane P, et al. Comparing usability of NEXThaler(®) with other inhaled corticosteroid/long-acting β2-agonist fixed combination dry powder inhalers in asthma patients. *J Aerosol Med Pulm Drug Deliv*. 2014;27(5):363-370.

165. Yildiz F. Importance of inhaler device use status in the control of asthma in adults: the Asthma Inhaler Treatment Study. *Respir Care*. 2014;59(2):223-230.

166. Sanchis J, Corrigan C, Levy ML, Viejo JL. Inhaler devices: from theory to practice. *Respir Med*. 2013;107(4):495-502.