Technical Evaluation of Soft Mist Inhaler Use in Patients with Chronic Obstructive Pulmonary Disease: A Cross-Sectional Study

Background: Proper inhaler technique is highly relevant to the effective management of chronic obstructive pulmonary disease (COPD). The tiotropium bromide spray (TBS) (Spiriva® Respimat®) is a soft mist inhaler (SMI) preferred by patients to pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) because of its convenience in use. However, the technique of using TBS inhaler in the real world is unclear.

Objective: To evaluate techniques in using TBS inhaler and investigate the association between the patient characteristics and the correct use of TBS inhaler.

Methods: This cross-sectional study enrolled 74 COPD patients who used TBS inhaler device for more than 3 months. The sociodemographic and clinical characteristics of the patients were recorded. The technique of using TBS inhaler was evaluated step by step. Incorrect use was defined as the patient’s inability to complete the key steps in the inhalation manoeuvre. The percentage of incorrect use was compared between the groups. Risk factors related to incorrect use were analyzed by logistic regression analysis.

Results: Of the 74 participants, only 2 (2.7%) patients completed all the steps correctly, and 48 (64.9%) patients misused the key steps in the inhalation manoeuvre. Incorrect preparation of the TBS inhaler for the first use was the most frequently misused step, accounting for 77.0%. Factors associated with misuse of TBS inhaler included the educational background (p=0.010), living state (p=0.031) and COPD assessment test (CAT) score (p=0.005) of the patients. Additionally, logistic regression analysis showed that the COPD duration was significantly associated with the incorrect use (p=0.019). Compared with patients with a higher educational background, patients with an elementary school background [OR 11652.99, CI: 22.72–5975697.72], junior high school background [OR 7187.78, CI: 3146787–16.41–3146787] and high school background [OR 1563, CI: 4.27–572329.67] were more likely to misuse TBS inhaler. Patients living with their spouses alone were also more likely to commit errors in using TBS inhaler as compared with those living with their children [OR 12.29, CI of 1.14–1.96]. Clinical factors like the COPD symptoms were relative to the technical use of the device. Better technique was accompanied by a lower CAT score [OR 1.49, CI of 1.14–1.96].

Conclusion: The incorrect use of TBS inhaler was common in COPD patients. Healthcare providers should not only teach the patients about the drug preparation but help them use the inhaler correctly. Special attention should be paid to patients with a short COPD duration and a low educational background and those who live without the company of their children. Proper use of TBS inhaler can significantly improve the symptom control of COPD patients.

Keywords: chronic obstructive pulmonary disease, inhaler technique, soft mist inhaler, incorrect use
Introduction

Chronic obstructive pulmonary disease (COPD) causes significant morbidity and mortality in elderly populations worldwide and is estimated to become the third highest cause of death by 2020.\textsuperscript{1} COPD is also one of the most significant health problems in China with a prevalence of 13.7% in the general Chinese population aged 40 years or older, causing more than 0.9 million deaths in 2013.\textsuperscript{2,3} Inhalation therapy is the mainstay of COPD management due to the advantage of targeting the drug directly to the respiratory system, thus reducing the risk of systemic adverse events.\textsuperscript{1}

The therapeutic outcome of a COPD drug depends not only on its pharmacological properties but also on the correct use of the inhaler on the part of the patient. However, incorrect use of inhaler devices is very common. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report states that more than two-thirds of patients make at least one error in using an inhalational device and there is a significant relationship between poor inhaler use and symptom control in COPD patients.\textsuperscript{4} Poor inhaler manipulation can decrease the dose effect of the medicine, lead to poor disease control, induce acute disease exacerbation, and reduce the patient’s quality of life.\textsuperscript{5,6} Factors related to inhaler misuse reported in the previous studies included older age, the use of multiple inhalers, low health literacy, low lung function, lack of knowledge about their disease, and lack of inhaler-use training.\textsuperscript{1,7}

There are three main types of inhalers, dry powder inhalers (DPIs), pressed metered dose inhalers (pMDIs), and soft mist inhalers (SMIs). Each type of inhalers has specificities on how to prepare the dose and need different techniques to deliver the drug to the airway. pMDIs need the patient to coordinate activation of the device while inhaling. DPIs generate drug aerosol by the patient’s inhalation, which needs patients to inhale forcefully and deeply to generate the necessary inspiratory flow within a range to enable optimum drug delivery. However, each type of inhaler devices has pros and cons. Capstick TGD et al reported that approximately 60% COPD patients and 92% asthma patients inhaled too fast from a pMDI.\textsuperscript{8} For DPIs, patients with severe airflow obstruction, pediatric patients and elderly patients may encounter the obstacle to generate appropriate inspiratory flow.\textsuperscript{9} Peak inspiratory flow through Accuhaler, Turbuhaler and Handihaler device was shown to be too slow in 4.9%, 14.2% and 57.0% COPD patients, respectively.\textsuperscript{5} The inhaler of tiotropium bromide spray (TBS) (Respimat\textsuperscript{®}, Spiriva) combines the advantages of pMDIs and nebulizers. It is a small, portable and hand-held inhaler without propellants. Individual doses are delivered via a precisely engineered nozzle system to produce a slow-moving and long-sustaining aerosol cloud (like nebulizers), thus greatly reducing the need to coordinate between actuation and inspiration like the pMDIs and bypassing the inspiratory flow limitation of the DPIs.\textsuperscript{10}

Selection of an appropriate inhaler for each patient has been advocated to be tailored by considering patients’ ability to use in the GOLD guideline. Recently, Chapman and coworkers proposed an algorithm approach to inhaler selection by taking into consideration the patient’s ability to generate an inspiratory flow rate >30 L/min when DPIs were used and to coordinate actuation and inspiration when pMDIs were used.\textsuperscript{10} By virtue of convenient use, TBS inhaler is recommended as the inhaler for patients with a poor inspiratory flow rate and coordination.\textsuperscript{11} In addition, several studies have demonstrated that TBS inhaler is most preferred by the patients as compared with other inhalers.\textsuperscript{12}

However, whether TBS inhaler is correctly used in the real world remains unclear. The aim of the present study was to evaluate the situation of using TBS inhaler in COPD outpatients in our hospital and explore the association between the patient features and incorrect use of the inhaler device.

Materials and Methods

This cross-sectional study was conducted between November 2019 and January 2020 at the outpatient department of Shanghai Pulmonary Hospital affiliated to Tongji University (Shanghai, China).

Participants and Design

The participants were male and female outpatients ≥40 years of age with a diagnosis of COPD. The inclusion criteria were patients with a duration of using TBS inhaler longer than 3 months and had their lung function tested in the previous year. The exclusion criteria were patients with a diagnosis of dementia, psychiatric disorders, parkinson’s disease, and other lung diseases such as asthma, idiopathic pulmonary fibrosis, pulmonary embolism, lung cancer, or chest deformity.
Ethical Statement

The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (Ethical Committee Approval No.: K20-004) and conducted in accordance with the Declaration of Helsinki. Patients who met the screening criteria provided written informed consent after being fully informed of the study purpose and procedures.

Study Parameters

Sociodemographic characteristics including age, sex, educational background, living state and smoking history were recorded using a pre-designed questionnaire form. Other clinical characteristics including the duration of COPD, duration of TBS inhaler use, and the source of technique training, comorbidities, accompanied inhalers, and the number of moderate or severe acute exacerbation in the preceding year were also obtained from the patients and their medical records. Moderate or severe acute exacerbation was defined as acute worsening of the respiratory symptoms resulting in additional therapies such as the use of short-acting bronchodilators (SABDs) plus antibiotics and/or oral corticosteroids, and in-hospital or emergency treatment. COPD was classified as mild, moderate, severe and very severe based on the forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) value from the spirometer. COPD assessment test (CAT) questionnaire was also used to assess the symptom control.

Inhaler Technique Assessment

The technique of using TBS inhaler was evaluated by using a detailed checklist. The checklist was developed according to the recommendations from the drug package inserts and reports in the published literature. \(^{12}\) The steps of TBS inhaler use evaluated in this study were divided into two stages: preparation and inhalation manoeuvre (Figure 1). The scoring standard was 1 point for each step completed by the patients, and 0 point for each step if there was an operation error by the patients. Each missed step was considered as an error. Incorrect use was defined as the patient being unable to complete any of the key steps in the inhalation manoeuvre at least. The key steps contained steps 6, 9 and 10. Two experienced
pharmacists were assigned to evaluate the step-by-step accuracy of TBS inhaler use. Any disagreement between the two pharmacists was resolved by discussion.

Statistical Analysis
The characteristics of patients in the study are presented by means of descriptive statistics. Differences in patient characteristics between the correct use group and incorrect use group were tested using the two-sample t-test and chi-square test. The odds ratio (OR) and 95% confidence intervals (CIs) were calculated using a logistic regression model to investigate the association between the patient characteristics and incorrect use of TBS inhaler. All statistical analyses were performed at a 5% level of significance. P < 0.05 was considered as statistically significant. All the analyses were conducted using SPSS software version 19.0.

Results
Patient Characteristics
The patient selection flow chart is presented in Figure 2. A total of 147 COPD patients from the outpatient department agreed to participate in the study. Of them, 26 patients who had used TBS inhaler less than 3 months were excluded, and the other 38 patients were further excluded due to lack of lung function testing. The number of patients with excluded comorbidities was totally 9, including 2 with asthma, 1 with idiopathic pulmonary fibrosis, 3 with pulmonary embolism, 2 with lung cancer and 1 with chest deformity. After multiple screening, 74 patients were finally eligible for inclusion in this study.

The sociodemographic and clinical characteristics of the 74 included patients are shown in Table 2. The mean age of the patients was 65.8 years with a male predominance (M/F 66/8). The number of patients with an elementary school, junior high school, high school and higher educational background was 14 (18.9%), 31 (41.9%), 21 (28.4%), and 8 (10.8%) respectively. Of them, 54 patients (73%) had a history of smoking, and 46 patients (62.2%) lived with their spouses alone. The mean duration of COPD was 7.9 years, and the mean duration of using TBS inhaler was 16.9 months. Most patients (56, 75.7%) inhaled Turbuhaler® as the accompanied drug, followed by Diskus®, Breezhaler® and Foster®. The proportion of patients who received training was 47.3% by doctors, 29.7% by nurses, 16.2% by the video, and 6.8% by reading the package insert. According to the FEV1% predicted, most patients had severe and very severe disease. The mean CAT score of the participants was 23.7±5.7. Approximately 77.0% of the participants exhibited acute exacerbation in the previous year.

Inhaler Techniques
The most frequent errors made by the participants with TBS inhaler are shown in Figure 3. Among the 74 patients, only 2 (2.7%) patients completed all the steps correctly. The three most frequently incorrect steps were “prepare TBS inhaler for first use” (77.0% made errors), “hold the inhaler vertically with the green cap closed to avoid accidental dose release” (66.2% made errors), and “hold breathing for 10 seconds or during the time that is possible with comfort” (48.6% made errors). As the key parameters of the assessment, 48 (64.9%) patients showed an incorrect use in the key steps. The percentage of incorrect use was 37.8%, 17.6% and 48.6% in steps 6, 9 and 10, respectively.

Association of Misuse with the Patient Characteristics
The educational background, living state and CAT score were significant factors associated with the inhaler technique (p=0.010, p=0.031 and p=0.005) (Table 1).

A binary logistic regression analysis showed that the duration of COPD (p=0.019), educational background (p=0.024),...
living state (p=0.032), and CAT score (p=0.004) were significantly associated with the inhaler technique (Table 2). Patients with a short duration of COPD increased the incorrect use rate of TBS inhaler [OR 0.80, CI 0.67–0.96]. Compared with the patients with a higher educational background, patients with an elementary [OR 116,99, CI 22.72–577,697.72], junior high school [OR 71,87, CI 16.41–314,678] and high school educational background [OR 15,63, CI 4.27–572,399.67] were more likely to misuse TBS inhaler. Patients who lived with their spouses alone were at a higher risk to commit the misuse of TBS inhaler than those who lived with their children [OR 12.29, CI 1.77–85.18]. Clinical factor-like COPD symptom was relative to the patient’s correct use of TBS inhaler. Better technique in the inhalation manoeuvre was accompanied by a lower CAT score [OR 1.49, CI 1.14–1.96].

Discussion
Since the advent of pMDI in 1956,13 inhaled drugs have become the cornerstone of treatment for chronic lung diseases such as asthma and COPD due to the need of smaller doses, faster onset of action and fewer systemic adverse effects.8,11 pMDIs have been widely used as they are relatively inexpensive and can deliver various medications until the CFC propellant of pMDI proved to deplete the ozone layer in the stratosphere in the 1970s. The DPIs quickly rise. Currently, both pMDIs and DPIs are the major inhalant devices for the treatment of asthma and COPD. However, problems emerged in the clinical use of these two types of inhalers. The difficulties with pMDIs are the need to coordinate activation of the device while inhaling. It was reported that the misuse of pMDI was very common. Al-Showair et al demonstrated that approximately 60% of patients with COPD were inhaling too fast from a pMDI.14 Rau JL reported that coordinate inhalation with actuation of the pMDI as the most frequency error with pMDI based on 12 studies involving 955 subjects.15 The challenge for DPI is that the patient should have enough inspiratory flow to disperse the powder,14 which is probably unable for children or elderly patients.16–18

TBS inhaler is a new generation inhaler, which is called a soft mist inhaler in that it can generate slow and long-lasting aerosol by mechanical power from a spring rather than a liquid-gas propellant. TBS inhaler has been thought to overcome the difficulties that patients may have in using pMDIs and DPIs,19 because it facilitates co-ordination of actuation and inhalation compared with pMDIs and does not need the patient to surpass the inspiratory flow threshold of DPIs. TBS inhaler is also designed to be used easily and considered to be user-friendliness.19,20 A number of studies have shown that most patients prefer the use of TBS inhaler to pMDI or DPI.21,22

Although TBS inhaler is thought to be used easily, only 2.7% of patients with COPD could complete all the steps correctly in this study. The most frequent problem was in the preparation process. Almost 77.0% of patients could not correctly operate the device for the first use and needed help from the healthcare workers or other care providers, even though they had used TBS inhaler for a long period. The most frequent error in this step was that the patients failed to release the aerosol three times before first use because they thought it a waste of the drug, not knowing...
Table 1 Patient Characteristics and Association with Inhaler Technique (n=74)

| Characteristics                        | n (%) | Correct Technique (n=26) | Incorrect Technique (n=48) | t-test (p-value) | χ² (p-value) |
|----------------------------------------|-------|--------------------------|---------------------------|-----------------|--------------|
| Age, years (mean±SD)                   |       |                          |                           |                 |              |
| <60                                    | 14 (18.9%) | 4                        | 10                        |                 | 0.790        |
| 60–69                                  | 40 (54.1%) | 14                       | 26                        |                 |              |
| ≥70                                    | 20 (27.0%) | 8                        | 12                        |                 |              |
| Gender                                 |       |                          |                           |                 |              |
| Male                                   | 66 (89.2%) | 24                       | 42                        |                 | 0.705        |
| Female                                 | 8 (10.8%)  | 2                        | 6                         |                 |              |
| Educational background                 |       |                          |                           |                 |              |
| Elementary school                      | 14 (18.9%) | 3                        | 11                        |                 | 0.010*       |
| Junior high school                     | 31 (41.9%) | 8                        | 23                        |                 |              |
| High school                            | 21 (28.4%) | 8                        | 13                        |                 |              |
| University                             | 8 (10.8%)  | 7                        | 1                         |                 |              |
| Smoking                                |       |                          |                           |                 |              |
| Never                                  | 13 (17.5%) | 4                        | 9                         |                 | 1.000        |
| Former                                 | 54 (73.0%) | 18                       | 36                        |                 |              |
| Current                                | 7 (9.5%)   | 2                        | 5                         |                 |              |
| Living state                           |       |                          |                           |                 |              |
| Lonely                                 | 4 (5.4%)   | 2                        | 2                         |                 | 0.031*       |
| With the couple                        | 46 (62.2%) | 11                       | 35                        |                 |              |
| With the children                      | 24 (32.4%) | 13                       | 11                        |                 |              |
| Duration of COPD, years (mean±SD)      | 7.9±6.6       | 8.7±7.3              | 7.5±6.2                  | 0.476          |
| Duration of TBS inhaler use, months (mean±SD) | 16.9±20.4     | 20.3±20.1             | 15.1±20.6               | 0.298          |
| Training style                         |       |                          |                           |                 |              |
| By doctors                             | 35 (47.3%) | 12                       | 23                        |                 | 0.943        |
| By nurses                              | 22 (29.7%) | 7                        | 15                        |                 |              |
| By the video                           | 12 (16.2%) | 5                        | 7                         |                 |              |
| By reading the package insert          | 5 (6.8%)   | 2                        | 3                         |                 |              |
| Accompanied inhaler                    |       |                          |                           |                 |              |
| Turbuhaler®                            | 56 (75.7%) | 20                       | 36                        |                 | 0.861        |
| Diskus®                                | 5 (6.8%)   | 1                        | 4                         |                 |              |
| Breezhaler®                            | 9 (12.2%)  | 3                        | 6                         |                 |              |
| Foster®                                | 4 (5.4%)   | 2                        | 2                         |                 |              |
| FEV1% predicted (mean±SD)              | 41.4±19.2    |                          |                           |                 |              |
| Mild                                   | 5 (6.8%)   | 2                        | 3                         |                 | 0.736        |
| Moderate                               | 16 (21.6%) | 6                        | 10                        |                 |              |
| Severe                                 | 30 (40.5%) | 12                       | 18                        |                 |              |
| Very severe                            | 23 (31.1%) | 6                        | 17                        |                 |              |
| CAT score (mean±SD)                    | 23.7±5.7     | 21.3±5.7             | 25.1±5.2                 | 0.005*         |
| Acute exacerbation                     |       |                          |                           |                 |              |
| Yes                                    | 57 (77.0%) | 17                       | 40                        |                 | 0.080        |
| No                                     | 17 (23.0%) | 9                        | 8                         |                 |              |

Notes: The numeration data are expressed as n (%) and the measurement data are expressed as mean ± standard deviation; The numeration data and measurement data were statistically analyzed with χ² test and t-test, respectively; * means that there was a significant distribution or difference between the correct technique group and incorrect technique group.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; SD, standard deviation; TBS, tiotropium bromide spray.
In the inhalation manoeuvre, step 6 “slowly and fully release the air from the lungs”, step 9 “while deeply and slowly breathing in by mouth, press the application button and continue to breathe in as slowly as possible during the longer time possible”, and step 10 “hold breathing for 10 seconds or during the time that is possible with comfort” ranked the top of incorrect use. According to the misuse rate of step 9 (17.6%), TBS inhaler has indeed reduced the mistake of incoordination of activation and inhalation in the inhalation pattern when using pMDIs (17.6% vs 60%). It was found in this study that the popular mistake in this step is aerosol leakage in some severe patients who were unable to maintain the breath as long as the duration of aerosol release. Due to the high price of TBS inhaler in China, the physicians prescribed TBS inhaler instead of tiotropium Handihaler® for patients with more severe disease on account of the high resistance of Handihaler® and the weak inspiratory flow of the patients, which is consistent with the finding that most participants in this study were patients with severe and very severe COPD. This result indicates that patients, especially those with severe and very severe COPD, should be evaluated in advance to determine whether TBS inhaler is suitable for them. The other two incorrect steps (steps 6 and 10) were often found with both pMDIs and DPIs in previous studies. Incompletion of step 6 decreases the patient’s inspiratory volume and affects the delivery of the inhaled drug. Breath-holding is important for aerosol deposition because it can increase the gravitational sedimentation for smaller particle sizes, which should be emphasized when the patients get the inhaler technique training.

Our study shows an association between incorrect use of TBS inhaler and the educational background, which has also been reported in many previous studies about pMDIs and DPIs. According to our observation, patients with a higher educational background concentrated more attention on the technique training process and were more willing and active to communicate with the trainers as compared with those with a lower educational background. Knowing that it is a common habit for parents to live with their children in China, we included this living state as a factor in our study. It was found that living with the children was beneficial to the correct use of TBS inhaler. The possible reason is that most COPD patients are old-aged and lack the knowledge about handling the inhaler correctly, and therefore they need constant and patient reminders and help from young persons to ensure the correct use of the inhaler. Patients with good symptom control scored by the CAT questionnaire had a good technique. This may be explained by the fact that better inhalation techniques allow more drugs to be delivered to the lung. This association between symptom control and inhaler technique has also been established in previous studies.

In addition to the educational background, the living state and CAT score, our logistic regression analysis showed that the duration of COPD was also a factor affecting TBS inhaler use. This finding may be related to the standard that we set for the correct inhaler use technique in our study. Completing the 3 steps is not only considered the correct technique in the inhalation manoeuvre of TBS inhaler but is also essential in using other inhalers. The longer the duration of COPD, the more likely the patients would be to use other inhalers, which helpful for them to handle the key steps of TBS inhaler use.

### Table 2 Logistic Regression of Patient-Related and Disease-Related Variables

| Variables          | p-value | OR  | 95% CI          |
|--------------------|---------|-----|-----------------|
| Duration of COPD   | 0.019*  | 0.80| 0.67–0.96       |
| Educational background | 0.024*  |     |                 |
| Elementary school  | 0.003*  | 11652.99 | 22.72–597569.72 |
| Junior high school | 0.004*  | 7187.78 | 16.41–314678.7  |
| High school        | 0.015*  | 1563 | 4.27–572329.67  |
| University         |         | 1862.79 | 1.14–306.05     |
| Living state       | 0.032*  |     |                 |
| Alone              | 0.605   | 0.46 | 0.02–8.86       |
| With the spouse    | 0.011*  | 12.29 | 1.77–85.18      |
| With the children  |         | 122.56 | 1.33–1165.46    |
| CAT score          | 0.004*  | 1.49 | 1.14–1.96       |

Notes: * means that there was a significant association of the variable with the inhaler technique; # means that there was a significant difference between the compared group and the reference group.

Abbreviations: CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds rate.
Age was considered to be the significant factor associated with the inhaler technique in some studies, but was also found to be insignificant in other studies. In this study, we failed to find a significant correlation between patient age and TBS inhaler use. The reason for these conflicting results may be due to differences in classification of the age range, the inhomogeneous distribution of participants in the age catalogue, and the scoring assessment. Liang et al found that age was not associated with the inhaler technique, in which the most of patients aged ≥70 years and the inhaler misuse was defined as an error in at least one step. Meanwhile, age was not related to the inhaler technique in another study, in which most patients ranged in age between 31 and 70 years and the good or poor inhaler technique mainly depended on the essential and non-essential steps. In our study, a high proportion of patients aged between 60 and 70 years, and the key steps in the inhalation manoeuvre were used as the criterion for evaluating the quality of TBS inhaler use.

**Limitation**

The sample size was small. According to the schedule, the study was conducted within 6 months. Regrettably, we were unable to continue with our patient interview from February 2020 because of the COVID-19 outbreak in China. In addition, we did not evaluate the technical use of the accompanied inhalation drugs due to the limited interview time acceptable by the patients. The misuse of the attached inhalation drugs may interfere with the result of symptom control. Despite these limitations, this study can still to some extent reflect the use of TBS inhaler in the real world and reminds healthcare workers and other providers to strength technical training of patients about the correct use of TBS inhaler.

**Conclusion**

The study has shown that incorrect use of TBS inhaler by COPD patients was common in the real world even though it was considered to bypass the problem of pMDIs or DPIs and was user-friendliness. Patients were more likely to commit errors during drug preparation and inhalation manoeuvre, which therefore should be highlighted by the healthcare workers or other providers in training the use of TBS inhaler. A short COPD duration, a lower educational background, and living without the company of their children are risk factors contributing to the incorrect use of TBS inhaler, all of which deserve attention during technical training, knowing that good use of TBS inhaler can significantly improve the symptom control of COPD patients.

**Funding**

This study was supported by Shanghai “medical new star” young medical clinical pharmacist training program and Subject support program of Shanghai Pulmonary Hospital.

**Disclosure**

The authors have no conflicts of interest in this work.

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