ORIGINAL RESEARCH

Correlation Analysis of the Therapy Adherence to Long-Acting Inhalers Among Patients with Stable COPD

Xin Tan[1],*, Shanling Liu[2],*, Li Huang [ID][3], Ying Wu[2], Long Wen[4], Jiheng Liu[5], Yuling Tang[4], Xiaohui Liu [ID][6]

[1]Department of Pediatric, The First Hospital of Changsha, Changsha, Hunan, People's Republic of China; [2]Department of Laboratory Medicine, The First Hospital of Changsha, Changsha, Hunan, People's Republic of China; [3]Department of Pharmacy, Zhuzhou Central Hospital, Zhuzhou, 412007, People's Republic of China; [4]Department of Respiratory and Critical Care Medicine, The First Hospital of Changsha, Changsha, Hunan, People's Republic of China; [5]Department of Hematology & Oncology, The First Hospital of Changsha, Changsha, Hunan, People's Republic of China; [6]Department of Pharmacy, The First Hospital of Changsha, Changsha, Hunan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaohui Liu, The First Hospital of Changsha, Department of Pharmacy, 311 Yingpan Road, Kaifu District, Changsha, 410005, People's Republic of China, Tel +86 731 84667573, Fax +86 731 84667680, Email gcys2021@126.com

Purpose: Long-acting inhalers are the mainstay maintenance therapy for stable chronic obstructive pulmonary disease (COPD) management. The aim of this study was to assess adherence to inhalers among adults with COPD in China and to develop strategies to improve adherence for the next step.

Patients and Methods: A cross-sectional study was conducted among 246 adult patients with COPD using long-acting inhalers to explore different demographic characteristics, disease characteristics and medication regimens. Adherence to inhalers was assessed using the Medication Adherence Report Scale (MARS).

Results: Among the 246 patients included in the present study, 93 (37.80%) had good adherence, while 153 (62.20%) had poor adherence. From the comparison of patients with good and poor adherence, we found that the course of disease and education background had a significant effect on adherence (p < 0.05). Among the LAMA therapy group, inhaled tiotropium bromide spray (Ingelheim am Rhein, Germany) with active release technology had better adherence than inhaled tiotropium bromide powder (Ingelheim am Rhein, Germany) (p < 0.05). Moreover, COPD patients with good adherence had better pulmonary function and fewer moderate or severe exacerbations in the past year (p < 0.05).

Conclusion: The factors affecting the use of inhalers in patients with stable COPD are complicated. Medical staff should select appropriate inhalers according to the patient's disease status and duration and provide medication education to improve adherence.

Keywords: chronic obstructive pulmonary disease, inhalers, adherence, duration of illness

Introduction

Chronic obstructive pulmonary disease (COPD) is a clinically frequent and common chronic disease characterized by incompletely reversible airflow restriction and persistent respiratory symptoms.[1] Currently, COPD is the third leading cause of death and the fifth leading economic burden in the world,[2,3] and the spirometry-defined prevalence of COPD in China in 2015 was 8.6%.[4] The Global Initiative for Chronic Obstructive Lung Disease recommends that the treatment of choice for long-term control of COPD is long-acting inhalers therapy.[5] Three main classes of drugs are commonly used alone and in combination to manage COPD: long-acting beta-adrenoceptor agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS). Poor adherence to inhaled therapy has now been clearly established as a main risk factor for the exacerbation of COPD and the effect on the hospitalization rate.[6,7] However, the adherent group had a lower all-cause cost and a lower COPD-related cost versus those of the poor-adherent group.[8]

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Although there are some studies focusing on the adherence and factors affecting inhaled medications in COPD patients,[9,10] they are inconclusive, and comprehensive systematic studies are lacking. Therefore, we collected data from patients with stable COPD to assess the patient adherence by the MARS and investigated the differences in patient adherence under different demographic characteristics, disease characteristics and medication regimens. We further analyzed the possible reasons for poor adherence, and made suggestions for improvement, meanwhile, aiming to provide some reference implications for the management strategies of patients with stable COPD.

Materials and Methods

Study Objects

This cross-sectional study was conducted in the First Hospital of Changsha from November 2020 to February 2021. The study enrolled patients ≥40 years old with spirometric confirmation of COPD[5] who had used any type of inhaler for more than 1 month. We excluded individuals diagnosed of other chronic respiratory diseases such as active pulmonary tuberculosis, lung tumor and pulmonary interstitial diseases, and were unable to communicate due to mental illness, impaired consciousness, psychological disorder, cognitive impairment, or other reasons. COPD patients who completed study period were finally analyzed as shown in Figure 1. The 246 patients used dry powder inhaler (DPIs) and soft mist inhaler (SMI). In this real-world study, we evaluated inhaler adherence and determinants of high adherence in patients.
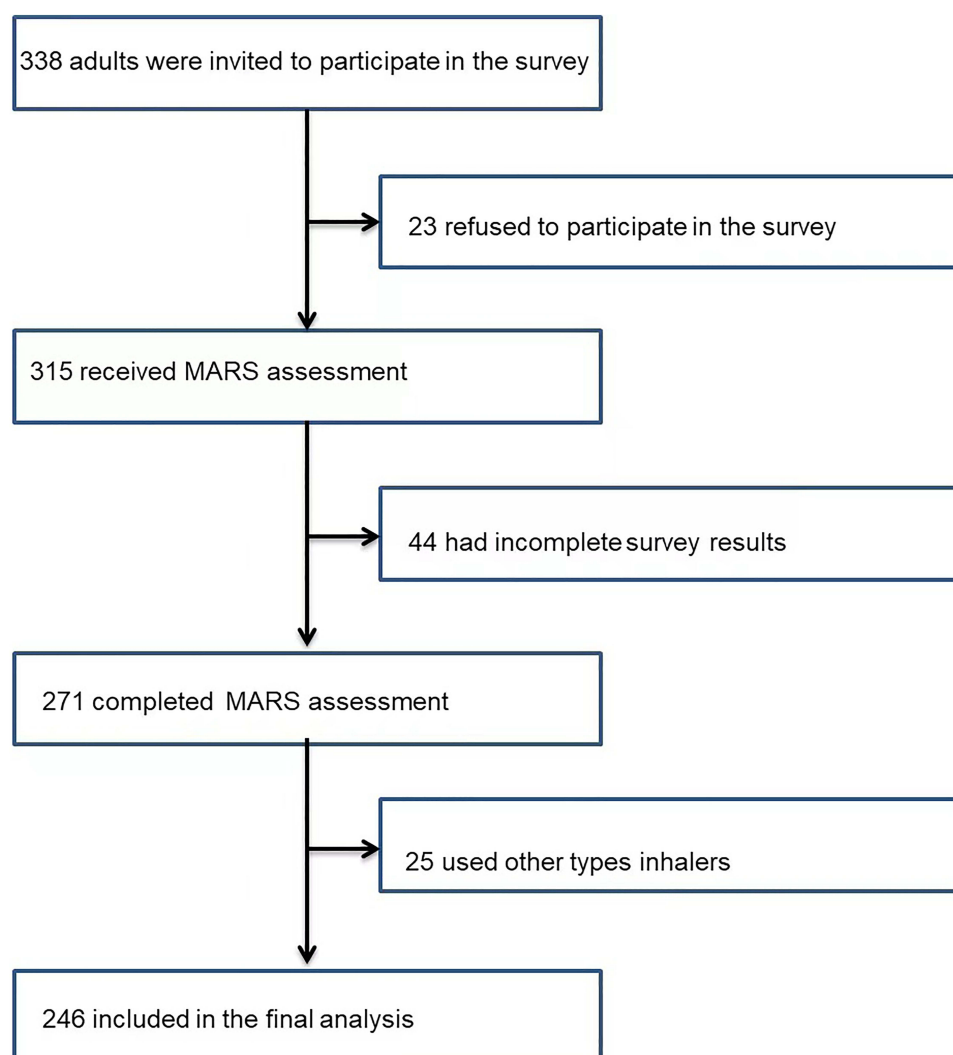

Figure 1 Flow of participants through the study.

Methods

A cross-sectional study was used to explore the differences in adherence among patients with different demographic characteristics, disease characteristics and medication regimens. After signing the informed consent forms, general information about the patients was registered, including name, gender, age, weight, education level, economic status, personal history, past history and duration of illness, number of hospitalizations due to acute exacerbation of COPD in the last year. All patients underwent spirometry and the post-bronchodilator percent predicted forced expiratory volume in the one second (FEV1) was used to determine disease severity.[5] Two clinical pharmacists conducted all of the interviews and assessed patients' adherence to inhalers according to the MARS, which is designed as questions based on negative statements to limit social desire bias,[11] had good interitem correlation (Cronbach alpha = 0.85 and 0.86, respectively) and good test-retest reliability (r = 0.65, P < 0.001).[12] Responses were scored on a 5-point Likert scale, ranging from always (1 point) to never (5 points). The total MARS score was calculated as the average of 10 specific scores. Good adherence was considered if the MARS score was greater than 4.5 which had a sensitivity of 51% and a specificity of 68%, and poor adherence if the MARS score was less than 4.5.[11]

This study was conducted in accordance with all relevant tenets of the Declaration of Helsinki. The protocol was approved by the Medical Ethics Committee (registration number kx-2020060) of the First Hospital of Changsha (China).

Statistical Analysis

According to the content of the questionnaire, data entry was performed using EpiData 3.0 software. After auditing, the data were imported into the SPSS 20.0 statistical package for statistical verification, sorting and analysis. Data with normal distribution and homogeneous variance were tested by *t*-test; uneven variance by corrected *t*-test; non-normal distribution by Mann Whitney *U*-test; count data by Chi square test or Fisher exact test. All tests were bilateral. Differences were considered statistically significant when p-values < 0.05.

Results

Subject Characteristics

In the study, 246 patients received inhalers with stable COPD completed the baseline survey and completed the MARS questionnaire. Among 246 patients, mean age was 70.9±9.6 years, and the majority of patients were male (82.1%). Mean duration of COPD was 7.8±6.6 years, 73.6% had two or more acute exacerbations in the previous year, and 58.9% had a history of smoking. Of the included patients, only 50 (20.3%) had graduated from high school or above, 22.4% of the households' average monthly income was higher than 3000 yuan (Table 1). The mean MARS score was 3.97±0.83. While 93 patients (37.80%) with MARS scores ≥4.5 had good adherence, 153 patients (62.20%) had poor adherence. There were no differences in gender, age, weight, income, smoking history and comorbidities between the two groups. However, there were statistically significant differences (p < 0.05) on education background, the duration of illness, moderate or severe exacerbation history in the past year and severity of airflow obstruction between them (Table 1).

Inhaled Medication

We divided the data into ICS/LABA and LAMA subgroups according to their pharmacological effects to analyze whether there was a difference in patient adherence if different categories of drugs were inhaled. According to Figure 2, there was a statistical difference when using different inhalers (χ^2=4.26, *p*=0.04), and the proportion of patients with good adherence using LAMA drugs was larger. ICS/LABA drugs include Budesonide and Formoterol Fumarate Powder for Inhalation (II) (Sodertalje, Sweden), and Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation (Evreux, France). The study found no significant differences between the MARS scores of patients using budesonide formoterol and salmeterol fluticasone (Table 2). Surprisingly, among the LAMA therapy group, there was a statistically significant difference in terms of adherence between inhaled

Table 1 Demographic Features of the Adherence in Patients with Stable COPD

Characteristic	n (%)	Good Adherence (n=93)	Poor Adherence (n=153)	t/Z	p-value
Male	202 (82.1%)	81(87.10%)	121(79.08%)	2.53	0.11
Age					
≥ 65 years old	186 (75.6%)	71(76.34%)	115(75.16%)	0.04	0.83
42–65years old	60 (24.4%)	22(23.66%)	38(24.84%)		
Weight (kg)	59.17±10.05	59.51±9.73	58.96±10.26	0.89	0.35
Education background					
Junior high school or below	196 (79.7%)	67(72.0%)	129(84.3%)	5.38	0.02
High school or above	50 (20.3%)	26(28.0%)	24(15.7%)		
Household income monthly (yuan)					
<3000 yuan	188 (76.4%)	65(69.90%)	123(80.4%)	3.54	0.06
>3000 yuan	58 (23.6%)	28(30.1%)	30(19.6%)		
Personal history					
Smoking history	145 (58.9%)	59(79.57%)	86(62.50%)	1.25	0.26
Drinking history	14 (5.7%)	5(5.38%)	9(5.88%)	0.03	0.87
Comorbidities					
Hypertension	89 (36.2%)	33(36.89%)	56(35.71%)	0.03	0.86
Coronary heart disease	105 (42.7%)	40(43.01%)	65(42.48%)	0.01	0.94
Cerebral vascular disease	23 (9.3%)	9(9.68%)	14(9.15%)	0.02	0.89
Diabetes	26 (10.6%)	7(7.53%)	19(12.42%)	1.46	0.23
Chronic gastritis	48 (19.5%)	23(24.73%)	25(16.34%)	2.60	0.18
COPD history					
Course of disease	7.85±6.59	6.63±2.26	8.69±3.81	3.62	0.02
≥2 moderate or severe exacerbation past year	181(73.6%)	61(65.59%)	120(78.43%)	4.91	0.03
Severity of airflow obstruction					
Moderate	50(20.3%)	27(29.03%)	23(15.03%)	7.04	0.03
Severe	156(63.4%)	52(55.91%)	104(67.97%)		
Very severe	40(16.3%)	14(15.05%)	26(16.99%)		
Number of varieties of inhalers used successively					
<2	168 (68.3%)	57(62.29%)	111(72.55%)	3.39	0.07
≥ 2	78 (21.7%)	36(38.71%)	42(27.45%)		

Abbreviations: Z, Kolmogorov–Smirnov Z; t, t-test.

tiotropium bromide powder (Ingelheim am Rhein, Germany) and tiotropium bromide spray (Ingelheim am Rhein, Germany), with better adherence when using the spray (Table 3).

Medication Adherence Rates

The majority of the patients (62.2%) reported low overall adherence. The MARS scores of the poor adherence patients ranged from 1 to 5, with a mean score of 3.45±0.62. Approximately half of the patients reported that they sometimes or often occurred the following situations: used the inhalers when needed (54.2%) [median (IQR): 3 (2)], or used them when they felt breathless (46.4%) [median (IQR): 4 (1)], or used them as a reserve if other treatment did not work (44.4%) [median (IQR); 4 (2)], or tried to avoid using them (53.6%) [median (IQR): 3 (1)]. In the medication dose adherence evaluation items, more than 50% participants reported that forgot to take the inhalers (66%) [median (IQR): 3 (1)], or took it less than instructed (61.4%) [median (IQR); 3 (1)], or stopped taking the inhalers for a while (62.1%) [median (IQR): 3 (2)], miss out a dose (53.6%) [median (IQR); 3 (1)]. The percentages of patients' engagements in each action of non-adherence and the mean score for each item are shown in Table 4.
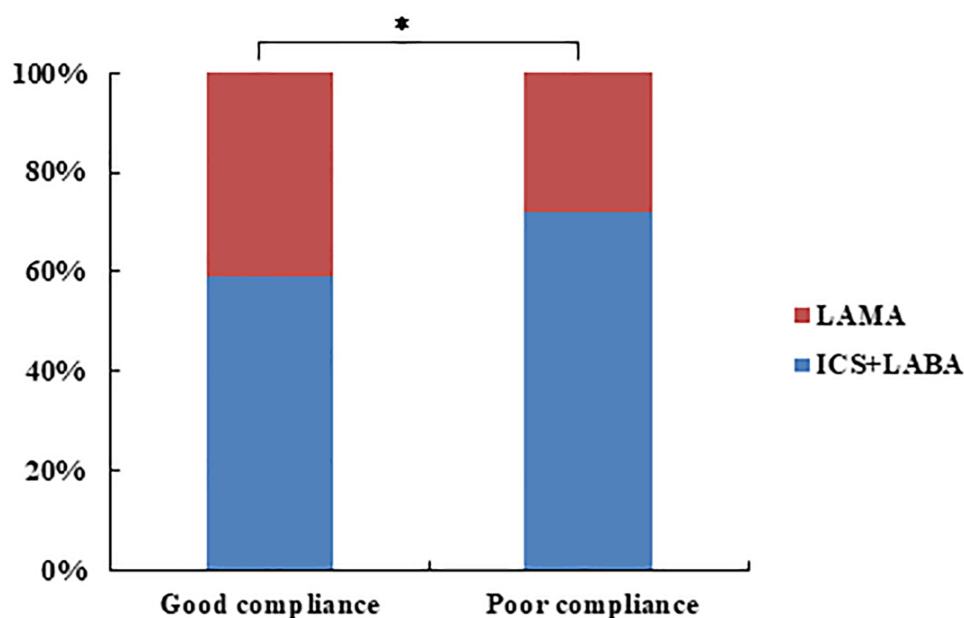
Figure 2 The comparison of different types of inhalers in patients with COPD. *$p < 0.05$.

Discussion
Adherence and Disease Regression

In this study, we analyzed the adherence to inhalers by using MARS score, a previously validated method, among patients with stable COPD. To our knowledge, there were no published studies using the similar method to assess the adherence to inhalers in China. Only 37.8% of the participants reported high adherence to inhalers. Although poor adherence to inhalers is common in the literature, the rate of poor adherence in this study was inconsistent with those reported in other studies.[11–14] Adherence with long-acting inhalers is considered to be the foundation of stable COPD treatment.[15,16] As our research results show, there were differences in the number of acute exacerbations and degree of airflow limitation severity in COPD patients with different adherence to inhalers. Previous research concluded similarly that subjects with complete adherence to therapy had a significantly lower FEV1 compared to those with low adherence.[17] Inhaled medication adherence is used to evaluate the extent to which patients take medication according to medical advice, including whether they are able to take medication consistently at the time, frequency and dose required by medical personnel, without changing medication at will.[16,18] Therefore, it is necessary to analyze the factors

Table 2 The Adherence of Patients Who Inhaled Different Drugs in ICS/LABA

Inhalant	Total Cases	Good Adherence	Poor Adherence	OR (95% CI)	*p*-value
Budesonide and Formoterol Fumarate	75	26(34.67%)	49(65.33%)	1.12 (0.58–2.14)	0.74
Salmeterol Xinafoate and Fluticasone Propionate	90	29(32.22%)	61(67.78%)		

Abbreviation: ICS/LABA, inhaled corticosteroids/long-acting beta-adrenoceptor agonists.

Table 3 The Adherence of Patients Who Inhaled Different Drugs in LAMA

Inhalant	Total Cases	Good Adherence	Poor Adherence	OR (95% CI)	*p*-value
Tiotropium Bromide powder spray	59	23(38.98%)	36(61.02%)	0.33 (0.12–0.95)	0.04
Tiotropium Bromide spray	22	15(68.18%)	7(31.82%)		

Abbreviation: LAMA, long-acting muscarinic antagonists.

Table 4 The Percentage of Patients' Engagements in Each Action of Adherence and the Mean Score for Each Item*

MARS Item	Always n (%)	Often n (%)	Sometimes n (%)	Rarely n (%)	Never n (%)	Mean (SD)	Median (IQR)
I only use it when I need it	13(8.5%)	57(37.3%)	44(28.8%)	33(21.6%)	6(3.9%)	3.25(1.01)	3(2)
I only use it when I feel breathless	30(19.6%)	52(34.0%)	37(24.2%)	29(19.0%)	5(3.3%)	3.48(1.11)	4(1)
I decide to miss out a dose	21(13.7%)	50(32.7%)	53(34.6%)	25(16.3%)	4(2.6%)	3.39(1.00)	3(1)
I try to avoid using it	30(19.6%)	41(26.8%)	53(34.6%)	26(17.0%)	3(2.0%)	3.45(1.05)	3(1)
I forget to take it	13(8.5%)	39(25.5%)	75(49.0%)	25(16.3%)	1(0.7%)	3.25(0.85)	3(1)
I alter the dose	23(15.0%)	57(37.3%)	48(31.4%)	22(14.4%)	3(2.0%)	3.49(0.98)	4(1)
I stop taking it for a while	18(11.8%)	40(26.1%)	56(36.6%)	29(19.0%)	10(6.5%)	3.18(1.08)	3(2)
I use it as a reserve, if my other treatment does not work	48(31.4%)	37(24.2%)	38(24.8%)	27(17.6%)	3(2.0%)	3.65(1.15)	4(2)
I use it before doing something which might make me breathless	78(51.0%)	37(24.2%)	27(17.6%)	10(6.5%)	1(0.7%)	4.18(0.99)	5(1.5)
I take it less than instructed	16(10.5%)	43(28.1%)	59(38.6%)	27(17.6%)	8(5.2%)	3.21(1.02)	3(1)
MARS-Score	Good adherence (Score≥4.5)					4.81(0.16)	4.90(0.20)
	Poor adherence (Score<4.5)					3.45(0.62)	3.49(0.92)
	Overall					3.97(0.83)	4.05(1.40)

Notes: *Items score, 5=Never, 4=Rarely, 3=Sometimes, 2=Often, 1=Always.
Abbreviation: MARS, Medication Adherence Report Scale.

influencing adherence to inhaled agents in stable COPD patients and to explore the possible and effective strategies to improve adherence.

Factors Influencing the Adherence

Medication adherence is influenced by several factors such as socioeconomic, health-care system, medical condition, therapy-related and patient-related.[19] Consistent with previous similar research,[14] we found that the patient's education background and the duration of illness had significant difference on the adherence with inhalers ($p < 0.05$). However, other observational studies considered no correlation was found between reported adherence and some of the demographic information.[20] We believe that stable COPD patients with higher education levels may have a better understanding of COPD and are more likely to adhere to inhalers to reduce COPD episodes. Patients with poor adherence to inhalers generally had a longer COPD course of disease in our study. With the prolongation of disease and the repeated use of inhaled preparations, their expectations for using inhalers to control the progression of the disease may decline, resulting in being reluctant to take medication as prescribed or even refusing medication. It has been reported that treatment adherence in patients with chronic airway disease gradually decreases with prolonged disease duration.[21] For these patients, medical staff need optimize treatment strategies and implement medication education covering the period of hospitalization and after discharge, then track through telephone follow-up, mobile phone applications and other new mobile management modes to further improve patients' treatment adherence.[5,18]

The inhaler device used to play a central role in the management of COPD.[16,22] Our analysis suggested that there were significant differences of patients adherence between inhaled ICS/LABA versus LAMA (p < 0.05) and tiotropium bromide powder for inhalation versus tiotropium bromide spray (p < 0.05). The potential reason is that tiotropium bromide spray uses a drug release technology to generate a fine, slow-moving mist, which only requires a lower inhalation velocity but need coordination actuation and inhalation, results in higher lung deposition (up to 50%) and oropharyngeal deposition lower, achieves better adherence, compared to pressurized metered-dose inhalers (pMDIs) and

DPI.[16,23,24] Some studies showed that patients using a pMDI inhaled ICS/LABA were 28% less likely to experience a COPD exacerbation-related hospital readmission within 60 days postdischarge compared with those using a DPI (OR: 0.72, 95% CI: 0.52–0.99, $P < 0.05$),[25] but our research had not been involved yet. In summary, inspiratory flow rate is a factor that physicians need to consider when choosing inhalers for their patients.[26] In the future, we will conduct continuous research to obtain more conclusions.

MARS Score

Our study showed that the mean MARS score was 3.97±0.83, which assessed our patients adherence to inhalers, indicating low adherence, which was close to that reported by other studies.[11,20] In this study, approximately half of the patients reported that they sometimes or often used the inhalers when needed or felt breathless, or used them as a reserve if other treatment did not work, or tried to avoid using them. They did not understand the necessity for adherence to therapy, indicating that a lack of understanding of the management knowledge of stable COPD may be the main reason for poor adherence to treatment.[27] For COPD patients, it is extremely important for telling them to adhere to standardized treatment during the stable phase.[5] In addition, in the medication dose adherence evaluation items, more than 50% participants reported that forgot to take the inhalers, or took it less than instructed, or stopped taking the inhalers for a while, miss out a dose. Our data showed a higher rate than other studies.[28,29] It also reflects patients in our study both intentional and unintentional non-adherence. On the one hand, current evidence suggests that the beliefs about medicines are more predictive of intentional non-adherence than of unintentional non-adherence.[30] It is necessary to consider using a patient accepted approach to repeatedly promote and educate patients about COPD disease knowledge and medication to help them build confidence in disease control. COPD guidelines recommend that inhaler training should be continually assessed at subsequent clinic visits. Where necessary, retraining should be provided.[5] Adherent patients were significantly more often trained with a demonstration, who were more often checked and more confident that the correct dose was taken, compared with nonadherent patients.[31,32] On the other hand, about the unintentional non-adherence, electronic dose monitoring was found to improve treatment adherence in chronic diseases.[33] Charles et al assessed patients using the MDI with an audiovisual reminder function (AVRF) were significantly less likely to "dose dump" (take multiple doses in a short time period) than the control group.[34] Yotaro Takaku considered it is necessary to repeat at least three times of instructions to achieve effective inhalation skills in COPD patients.[35]

This study also has some limitations: (1) there are many factors affecting inhalers adherence to COPD treatment such as health-care system, patients' general level of cognitive functioning, multi drug treatment and the techniques in using inhalation devices, which were not all included in, so logistic regression analysis was not done. (2) The MARS was based on patient reports, captured patient's general behaviors at the time of the baseline interview, and may have overestimated medication adherence due to issues with recall. Patients were from older adults with COPD, more likely to experience problems with memory than younger patients without these conditions. (3) The present study was limited by the small sample size. However, the relevant results can still be used as baseline data to provide a reference for further regulating stable COPD management and improving patients' treatment adherence.

Conclusion

In conclusion, overall adherence to long-acting inhalers for COPD is poor. Poor adherence to inhalers in COPD patients is likely associated with many factors, such as lower education level, long duration of disease and the type of inhalers. Moreover, COPD patients with poor adherence had worse pulmonary function and more episodes. This study suggests that for patients with stable COPD, proper inhaler device should be selected for patients. The findings of this study could help develop interventions designed to increase adherence to long-acting inhaled medications. Medical personnel should focus on the disease itself and the importance of medication adherence, implement medication education covering the whole period and strengthen follow-up of patients to track their condition and medication use, thus improving adherence with inhaler use and improving the quality of life of patients with stable COPD.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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