

Determinants of ICS Therapy Adherence in Patients With Asthma

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Asthma is a common chronic respiratory disease characterized by airway inflammation, airway hyperresponsiveness, and airway remodeling.¹ It is a public health problem that causes increasing mortality and disability.² By 2025, there will be 400 million patients with asthma in the world.³ Asthma has a negative impact on the quality of life of patients with the disease and leads to an increase in social and economic burdens.³ In recent years, the incidence of asthma in China has been rising. A national epidemiological survey from 2012 to 2015 showed that the total prevalence of asthma in China was 4.2%.⁴ At present, asthma prevention and control are significant challenges in China.

Inhaled drugs, the main treatment for asthma, can significantly improve asthma control.^{5,6} However, uncontrolled asthma is still common and a considerable burden for patients and society.⁷⁻⁹ An important reason for poor asthma control—and, therefore, for rising costs of health care—is suboptimal adherence to prescription regimens.¹⁰⁻¹³ Study findings have shown that the rate of inhaled glucocorticosteroid (ICS) adherence is less than 50% in adults.¹⁴⁻¹⁷ A survey based on the Australian Tasmanian cohort study reported that only 28% of patients with moderate persistent asthma and 48% of patients with severe persistent asthma were using ICS treatments regularly.¹⁵ In fact, poor patient adherence is the most frequently mentioned challenge (by 41% of physicians) in the treatment of asthma.^{9,18}

The adherence of patients with asthma to ICS or ICS/long-acting inhaled β_2 agonist (LABA) treatment depends on a number of factors that are closely related to the patient's economic status, social status, and culture. Although some studies have reported risk factors or determinants of poor adherence in Chinese patients with asthma,^{19,20} there is very limited evidence for the determinants of adherence to inhaled asthma-control therapy across different age groups. It is still necessary to conduct in-depth research, especially to understand the reasons for poor adherence from the patient's perspective.

ABSTRACT

OBJECTIVES: This study aimed to evaluate factors affecting adherence to inhaled therapy in patients with asthma to further identify the determinants most closely associated with adherence to inhaled therapy for asthma, especially inhaled glucocorticosteroids (ICS).

STUDY DESIGN: A 2-stage study was conducted. In stage 1, we performed nonassumptive deep-dive qualitative scoping to investigate the determinants of poor adherence in patients with asthma, and in stage 2 we developed a new questionnaire for cross-sectional surveys to obtain more accurate information about critical issues related to asthma management.

METHODS: Patients with asthma who were 18 years and older in the outpatient clinic of The First Affiliated Hospital of Xi'an Jiaotong University from November 2016 to January 2018 were investigated.

RESULTS: In the 350 patients with asthma recruited, 32% of patients showed good adherence, whereas 68% of patients displayed poor adherence to inhaled therapy due to various reasons. Further analysis indicated that inadequate understanding of asthma treatment and control, poor self-management, financial burden, adverse reactions, and the fear of potential adverse reactions were significant independent risk factors for poor ICS inhalation adherence in patients with asthma.

CONCLUSIONS: Our research shows that many patients with asthma in western China have poor disease control and poor inhalation therapy adherence. We hope this research can alert clinicians and help them identify patients who may be experiencing uncontrolled asthma due to poor adherence to inhaled therapy, and we suggest that clinicians help those patients obtain appropriate information about asthma control and self-management.

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METHODS

Objectives

The study aimed to evaluate factors affecting adherence to ICS therapy in patients with asthma to further identify the determinants most closely associated with adherence to inhaled asthma-control therapy. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (approval No. 2016-409).

Study Design

This study included 2 stages: Stage 1 was a structured patient interview, and stage 2 was a cross-sectional survey. In stage 1, 40 patients with inadequate asthma control were invited to participate in a 1-time face-to-face interview. We interviewed patients or their guardians within the framework of 5 categories, which were summarized based on publications and the specific characteristics of Chinese society, including therapy-related factors, patient-related factors, provider-related factors, disease-related factors, and practice- and system-related factors. Then, all the factors reported by patients in stage 1 were collected and analyzed, and the top 10 factors were incorporated into the paper questionnaire (case report form [CRF]) of stage 2 to further explore the risk factors affecting patients' adherence to inhalation therapy. In stage 2, 350 outpatients with asthma who were 18 years or older and who visited a respiratory or asthmatic outpatient clinic in the First Affiliated Hospital of Xi'an Jiaotong University were invited to participate in a face-to-face interview. Each patient was interviewed only once, and informed consent and all information collection were completed at the time of visit.

Inclusion Criteria

In each study site, outpatients who met all the following criteria were included: (1) were 18 years or older, (2) lived in the same city as the study site for at least 2 years, (3) had a history of at least 1 year of diagnosed asthma based on the criteria established by the Global Initiative for Asthma (GINA), (4) had inhaled ICS or ICS/LABA treatment in the past 6 months, and (5) were willing to sign the informed consent form.

Exclusion Criteria

Outpatients who met any of the following criteria were excluded: (1) patients with active cardiac or pulmonary disease (eg, bronchiectasis, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary tuberculosis, lung cancer, severe heart disease) or other disorders (eg, HIV/AIDS), or patients undergoing therapy that, according to their physician, would interfere with the aim of the study; (2) patients with mental or neurological disorders, or those who were unable to understand and honestly answer questions due to alcohol or substance abuse, or those who refused to answer

TAKEAWAY POINTS

- ▶ Patients with asthma in western China have poor disease control and poor inhalation therapy adherence.
- ▶ Inadequate understanding of asthma treatment and control, poor self-management, financial burden, adverse reactions, and the fear of potential adverse reactions were significant independent risk factors for poor adherence to inhaled glucocorticosteroid therapy in patients with asthma.
- ▶ This research may alert clinicians and help them identify patients who may be experiencing uncontrolled asthma due to poor adherence to inhaled therapy.
- ▶ Clinicians should help patients obtain appropriate information about asthma control and self-management.

questions; and (3) patients with other conditions judged by the investigators as unsuitable for this study.

CRF Survey in Stage 2

Related factors (10 determinants explored from stage 1) affecting adherence to inhaled therapy were collected; to fill out the CRF in stage 2, each of the 350 patients was asked to choose "yes" or "no" for each of the 10 items. Then, all data were inputted into the online electronic questionnaire data capture system by the investigator(s), and the valid data were included in the statistical analysis.

Adherence Rate Assessment

The Medication Adherence Report Scale for Asthma (MARS-A) questionnaire is a self-reported measure of adherence to inhaled therapy. The MARS-A scale has 10 questions; it assesses intentional and unintentional nonadherence. Patients completed the scale based on their medication adherence over the past 4 weeks, and the investigator calculated the total score for each patient based on the scale. According to the score, asthma medication adherence status was divided into 2 levels: good adherence (≥ 45 points) and poor adherence (< 45 points).

Asthma Control Assessment

The Asthma Control Test (ACT) was used to assess asthma control over the past 4 weeks. A score less than or equal to 19 was considered to signify asthma that was out of control. Scores greater than 19 but less than 25 were considered to signify partial control. A global score of 25 indicates complete control of asthma.

Statistical Analysis

Descriptive statistics were used to summarize the study characteristics and adherence measurement. Continuous variables were presented as the mean and SD, whereas categorical variables were presented as proportions. Variables were entered into a final model using a multivariate logistic regression analysis to identify significant factors associated with asthma medication adherence status. All statistical tests were 2-sided; a P value $< .05$ was considered significant. All statistical analyses were performed using SPSS 22.0 software (IBM).

TABLE 1. Characteristics of the Study Population

Characteristics	Study population, n (%)
Gender	
Male	128 (36.6%)
Female	222 (63.4%)
Age in years	
18-30	59 (16.9%)
31-45	95 (27.1%)
46-60	59 (16.9%)
> 60	137 (39.1%)
Disease history in years	
1-10	138 (39.4%)
11-20	22 (6.3%)
21-30	51 (14.6%)
31-40	50 (14.3%)
41-50	23 (6.6%)
51-60	58 (16.6%)
61-70	8 (2.3%)

TABLE 2. Univariate Logistic Regression Analysis of ICS Treatment Adherence in Patients With Asthma

Characteristic	Univariate analysis, OR (95% CI)	P
Gender	0.676 (0.419-1.093)	.11
Age	0.715 (0.013-1.475)	.057
Disease history	1.067 (0.836-1.363)	.602

ICS, inhaled glucocorticosteroid; OR, odds ratio.

TABLE 3. Main Reasons for Poor Adherence to Inhaled Treatment in Patients With Asthma

Characteristic	Number of patients (%)
Patients believed that their condition had been controlled or cured	185 (52.9%)
Patients used inhaled therapy only when asthma symptoms worsened or they had acute asthma attacks	160 (45.7%)
Patients' fear of potential adverse reactions	106 (30.3%)
Patients forgot inhaled treatment	88 (25.1%)
Due to financial burden	53 (15.1%)
Patients forgot to replenish with new drugs	43 (12.3%)
Inability to obtain adequate drug information due to insufficient communication with doctors	42 (12.0%)
Patients had an adverse reaction after using inhaled therapy	41 (11.7%)
The effect of inhaled treatment was considered slow or the effect was not significant after treatment	35 (10.0%)
Inhalation device operation was considered cumbersome or complicated	34 (9.7%)

RESULTS

Study Characteristics

As shown in **Table 1**, 350 participants were recruited in stage 2 of this study. Among them, 128 (36.6%) were men and 222 (63.4%) were women. The patients were aged between 18 and 84 years, with a mean (SD) age of 43.80 (15.59) years. Among the patients, 59 (16.9%) were aged 18 to 30 years, 95 (27.1%) were aged 31 to 45 years, 59 (16.9%) were aged 46 to 60 years, and 137 (39.1%) were older than 60 years. The asthma duration of the included patients ranged from 1 to 70 years, with a mean (SD) duration of 19.51 (18.82) years. Univariate logistic statistical analysis showed no significant difference in gender, age, and duration of treatment for ICS adherence in asthma patients ($P > .05$) (**Table 2**).

Status of Adherence to Inhaled Therapy

Among these 350 outpatients with asthma included in this study, some patients discontinued ICS treatment for various reasons. According to the MARS-A questionnaire scores, 238 (68%) of the 350 patients had poor adherence to inhaled therapy and 112 (32%) had good adherence. The top 10 determinants explored from stage 1 are listed in **Table 3**, and according to the CRF survey in stage 2, 52.9% of included patients believed that their condition had been controlled or cured, so they stopped using ICS or ICS/LABA therapy; 45.7% of patients used inhaled therapy only when their asthma symptoms were worsening or asthma was in acute attack; 30.3% of patients were afraid of potential adverse reactions, which means that these patients had suspended their treatment due to concerns about possible adverse effects of ICS treatment; 25.1% of patients had poor adherence due to forgetting to use inhaled treatment; and 15.1% of patients were unable to afford medicine because of the financial burden. In addition, other factors could also affect ICS treatment adherence in patients with asthma. For example, patients forgot to replenish with new drugs after the existing inhaled drugs were used up (12.3%); patients were unclear about the reasonable dosage, frequency, and course of inhaled treatment due to insufficient communication with doctors (12.0%); patients had an adverse reaction (eg, fungal infection of the oropharynx; hoarseness and cough due to respiratory tract irritation) after using inhaled therapy (11.7%); inhalation therapy was considered ineffective by the patient and was abandoned because the effect of inhaled treatment was not fast or not significant after treatment (10.0%); and patients were reluctant to use inhalation therapy because inhalation device operation was considered cumbersome or complicated (9.7%). At the same time, our study found that some patients had multiple risk factors that affected their treatment adherence. Among the included outpatients, 68 (19.4%) reported 2 risk factors affecting their inhaled treatment adherence, 59 (16.9%) reported 3 risk factors, and 81 (23.1%) reported 4 or more risk factors.

Determinants of ICS Treatment Adherence

To further clarify the independent risk factors affecting adherence to inhaled ICS therapy for asthma, we performed a multivariate logistic

regression analysis. As shown in **Table 4**, the multivariable analysis indicated that independent risk factors lowering the odds of ICS therapy adherence were patients believing that their condition had been controlled or cured (odds ratio [OR], 0.28; 95% CI, 0.16-0.48; $P < .01$), patients using inhaled therapy only when asthma symptoms were worsening or asthma was in acute attack (OR, 0.26; 95% CI, 0.15-0.46; $P < .01$), patients being unable to bear the financial burden (OR, 0.36; 95% CI, 0.17-0.75; $P < .01$), patients having adverse reactions after using inhaled therapy (OR, 0.26; 95% CI, 0.08-0.81; $P = .02$), and the fear of potential adverse reactions (OR, 0.59; 95% CI, 0.49-0.95; $P = .04$).

Determinants Across Age Groups

In the study, included outpatients were divided into groups according to age. To further investigate the most significant independent risk factor affecting ICS therapy adherence in patients of different age groups, we performed a subgroup multivariate logistic regression analysis based on age. As shown in **Table 5**, subgroup multivariate analysis showed that forgetting to use inhaled drugs for a variety of reasons was the most significant independent risk factor lowering the odds of inhaled therapy adherence in patients aged 31 to 45 years (OR, 0.33; 95% CI, 0.10-0.91; $P = .04$). Meanwhile, insufficient communication with doctors leading to the inability to obtain adequate drug information was the most significant independent risk factor lowering the odds of inhaled therapy adherence in patients older than 60 years (OR, 0.29; 95% CI, 0.10-0.86; $P = .03$). However, we did not find significant independent risk factors affecting inhaled therapy adherence in patients aged 18 to 30 years and aged 46 to 60 years ($P > .05$).

Determinants Across Asthma Control Status

Of the 350 outpatients with asthma included in the study, most patients had poorer disease control. According to the ACT score, 119 (34%) patients had asthma that was completely out of control, 201 (57.4%) patients had asthma that was partially controlled, and only 30 (8.6%) patients reported complete control of their condition. To further clarify the most significant independent risk factor for ICS therapy adherence in patients with different asthma control status, we performed a subgroup multivariate logistic regression analysis. The logistic analysis indicated that adverse reaction was the most significant independent risk factor lowering the odds of inhaled therapy adherence in patients whose asthma was completely out of control (OR, 0.03; 95% CI, 0.01-0.58; $P = .02$). However, in patients who reported partially controlled or fully controlled asthma, we did not find significant independent risk factors affecting adherence to inhaled therapy (data shown in the **eAppendix Table** [available at ajmc.com]).

DISCUSSION

To our knowledge, this is the first study to assess the determinants of ICS adherence among outpatients with asthma in western China from the patient's perspective. Asthma is a common chronic

TABLE 4. Multivariate Logistic Regression Analysis of ICS Treatment Adherence in Patients With Asthma

Characteristics	Multivariate analysis, OR (95% CI)	P
Patients' fear of potential adverse reactions	0.594 (0.492-0.947)	.044
The effect of inhaled treatment was considered slow or the effect was not significant after treatment	0.730 (0.218-1.898)	.519
Patients had an adverse reaction after using inhaled therapy	0.257 (0.081-0.813)	.021
Patients believed that their condition had been controlled or cured	0.277 (0.160-0.480)	<.001
Patients used inhaled therapy only when asthma symptoms worsened or they had acute asthma attacks	0.260 (0.146-0.463)	<.001
Due to financial burden	0.360 (0.172-0.754)	.007
Inhalation device operation was considered cumbersome or complicated	0.469 (0.166-1.330)	.155
Inability to obtain adequate drug information due to insufficient communication with doctors	0.689 (0.259-1.830)	.454
Patients forgot to replenish with new drugs	1.170 (0.405-3.381)	.772
Patients forgot inhaled treatment	0.943 (0.462-2.048)	.973

ICS, inhaled glucocorticosteroid; OR, odds ratio.

TABLE 5. Multivariate Logistic Regression Analysis of ICS Treatment Adherence in Patients With Asthma of Different Age Groups

Risk factors	Multivariate analysis, OR (95% CI)	P
Patients forgot inhaled treatment		
18-30 years	2.564 (0.361-18.229)	.347
31-45 years	0.325 (0.102-0.914)	.043
46-60 years	0.247 (0.030-2.010)	.191
> 60 years	0.907 (0.367-2.242)	.832
Inability to obtain adequate drug information due to insufficient communication with doctors		
18-30 years	*	.994
31-45 years	1.424 (0.347-5.839)	.624
46-60 years	*	*
> 60 years	0.289 (0.098-0.855)	.025

ICS, inhaled glucocorticosteroid; OR, odds ratio.

*Unable to calculate due to insufficient data.

respiratory disease worldwide, and it is reported that there will be 400 million patients with asthma in the world by 2025.^{1,3} Uncontrolled asthma is common and represents a considerable burden to patients and society in western China,⁴ so it is necessary to have an in-depth understanding of the current state of asthma treatment and asthma control.

The GINA guideline has indicated that ICSs are currently the most effective anti-inflammatory medications for the treatment of

persistent asthma, although they do not actually cure asthma.^{6,21-26} Compared with noninhaled administration, the ICS can be delivered directly into the airways, producing higher local concentrations with a significantly lower risk of systemic adverse effects.⁶ Meanwhile, LABA combined with ICS will usually be more effective when a medium dose of ICS alone fails to achieve control of asthma.²⁷⁻²⁹ Therefore, for patients with asthma, adherence to inhaled therapy is very important for controlling their condition. However, uncontrolled asthma is still a common phenomenon among outpatients with asthma.⁹ ICS or ICS/LABA treatment adherence in patients with asthma depends on a number of factors that are closely related to the patient's economic status, social status, and culture.

Nonadherence to medical advice is common in patients with asthma and is a major cause of uncontrolled asthma. Failure to adhere to medical advice is a complex social issue in western China. Exploring patients' cognition and drug preference status for their asthma treatment from their perspective can help establish effective doctor-patient relationships and improve asthma treatment adherence. In this study, our results showed that most outpatients with asthma had poorer disease control, and only 8.6% of patients reported complete control of their condition. According to the MARS-A questionnaire, 68% of the patients reported poor adherence to ICS therapy due to various reasons. The multivariate logistic regression analysis indicated that the belief that their condition had been controlled or cured, using inhaled therapy only when asthma symptoms were worsening or asthma was in acute attack, financial burden, adverse reactions after using inhaled therapy, and the fear of potential adverse reactions were the significant independent risk factors associated with ICS treatment adherence. Further subgroup analysis indicated that forgetting inhalation therapy for a variety of reasons was the most significant independent risk factor associated with inhalation treatment adherence in patients aged 31 to 45 years, and the inability to obtain adequate drug information due to insufficient communication with doctors was the most significant independent risk factor in patients older than 60 years. Additionally, our results indicated that an adverse reaction was the most significant independent risk factor associated with ICS therapy adherence in patients whose asthma was completely out of control. Therefore, based on our results, we recommend that clinicians should help those patients obtain appropriate information about asthma control and self-management, and should instruct those patients not to stop ICS or ICS/LABA irregularly. Meanwhile, effective replacement treatment is necessary and important for patients with adverse reactions after inhaled therapy. If clinicians understand the risk factors affecting asthma treatment adherence from the patient's perspective, they can use patient-centered communication skills to improve patients' adherence to asthma treatment and improve their asthma control.

Limitations

This study had some weaknesses. First, only 350 outpatients with asthma from one tier-3 hospital in western China were recruited

in this research. This is not enough to ascertain the exact extent of nonadherence to inhaled treatment in the whole population of patients with asthma. Secondly, asthma is a complex disease with many therapeutic medicines,^{1,30-32} including ICS,²¹ leukotriene modifiers,^{33,34} LABA,^{35,36} theophylline,^{37,38} rapid-acting inhaled β_2 agonists, and so on.⁶ Our study focused only on the current status of ICS or ICS/LABA in asthma control and did not further explore the role of other drugs in asthma control. When considering these limitations, the results of this research should be interpreted carefully.

CONCLUSIONS

This study's findings indicate that there are multiple independent risk factors that influence ICS therapy adherence in patients with asthma, including inadequate understanding of asthma treatment and control, poor self-management, financial burden, adverse reactions, and the fear of potential adverse reactions. Thus, we hope this research can alert clinicians and help them identify patients who may be experiencing uncontrolled asthma due to poor adherence to ICS therapy. We suggest that clinicians should help those patients obtain appropriate information about asthma control and self-management. For patients with adverse reactions after ICS therapy, effective replacement treatment is strongly recommended. ■

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eAppendix Table. Multiple Logistic Regression Analysis of ICS Treatment Adherence in Patients With Asthma With Different Disease Control States

Risk factors	Multivariate analysis, OR (95% CI)	<i>P</i>
Patients had an adverse reaction after using inhaled therapy		
Completely controlled	^a	^a
Partially controlled	1.626 (0.507-5.211)	.414
Out of control	0.028 (0.011-0.581)	.021

ICS, inhaled glucocorticosteroid; OR, odds ratio.

^aUnable to calculate due to insufficient data.