Adherence to Inhalers and Associated Factors Among Adult Asthma Patients: an Outpatient Based Study in a Tertiary Hospital of Rajshahi, Bangladesh

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Abstract

Background: Adherence to inhaler medication is an important contributor of optimum asthma control along with adequate pharmacotherapy. The objective of the present study was to assess self-reported adherence level and to identify the potential factors associated with non-adherence to the inhalers among asthma patients.

Methods: This facility-based cross-sectional study was conducted in the medicine outpatient department of Rajshahi Medical College Hospital from November 2020 to January 2021. A total of 357 clinically confirmed adult asthma patients were interviewed. Inhaler adherence was measured using the 10-item Test of Adherence scale (TAI). Both descriptive and inferential statistics were used to express the socio-demographic of the patients and predictors of poor adherence to inhaler.

Results: A substantial number of participants were non-adherent (86%) to inhaler medication. Patient non-adherent to inhaler medication are often younger (23.15, 95% CI 3.67-146.08), lived in rural area (23.28, 95% CI 2.43-222.66), less year of schooling (5.69, 95% CI 1.27-25.44), and belonged to the middle income (aOR 9.74, 95% CI 2.11-44.9) than those adherent with inhaler. Presence of comorbidities (12.91, 95% CI 1.41-117.61), prolonged duration of inhaler intake (5.69, 95% CI 1.22-26.49), consulting non-qualified practitioners (13.09, 95% CI 3.10-55.26) were the significant contributor of non-adherence.

Conclusion: Despite ongoing motivation and treatment, non-adherence to inhalation anti-asthmatic is high and several factors have been found contributed. Regular monitoring and a guided patient centered self-management approach might be helpful to address the in long run.

Background

Asthma is a heterogeneous chronic inflammatory obstructive bronchial disease which is mostly reversible and commonly presented with cough, rhonchus, wheezing, chest tightness, shortness of breath, and expiratory flow limitation (1). Globally more than 339 million people are suffering from this chronic respiratory disease resulting in 250 thousand deaths annually (2). The prevalence is increasing by fifty percent every decade, especially in the low and middle income countries of South-East Asian region (3,4). In Bangladesh, a lower-middle income country of this region, more than eight million people are suffering from asthma that constitutes almost 5.2% of the total population (5).

Successful asthma management depends on several drug and patient related factors like age, smoking, environmental and occupational factors, asthma related comorbidities, choice of drug and device, patients' adherence to the prescribed medications and their inhaler handling techniques (6). Inhalation therapy remains the mainstay of the asthma management mostly due to their rapid onset of action, high therapeutic efficacy and lower systemic adverse effects (2,6,7). Inhaled corticosteroids along with short or long acting beta-2 agonists and/or anti-cholinergic agents are most commonly prescribed as the first line treatment for controlling asthma (7). However, despite adequate pharmacotherapy, the control of asthma often has shown suboptimal as only prescribing appropriate medication is not adequate for achieving optimum asthma control. The Global Strategy for Asthma Management and Prevention adopted by the Global Initiative for Asthma (GINA) recommended a patient-care giver partnership and guided self-management, along with adequate drug therapy for achieving long term control and decreasing the frequency of exacerbation of asthma (2). In this patient-centered approach, increasing adherence to the prescribed inhalation therapy is highly emphasized as it was evidenced that almost half of the patients with chronic diseases fail to take their long-term medications as directed at least part of the time (2,8). Non-adherence to the prescribed medications is an important contributor of the uncontrolled asthma as well as increased healthcare utilization and increased cost (9–11).

(2). The rate of adherence varies across the country and also exists in between the age and sex groups (12). Almost 43% of the asthma patients worldwide are non-adherent to their inhalation therapy (13). However, some studies suggest that the rate may be as high as 87% among patients with severe asthma (14,15). A number of personal and socio-economic factors including patients' perception about the disease and medications, fear of side effects, patient-provider communication quality, family and social support as well as cost and availability of the drugs may influence the adherence of patients to their prescribed treatment (10,11,13).

Addressing non-adherence to the inhalation therapy should be a priority in the clinical assessment of asthma patients, especially who have difficult-to-control asthma and addressing non-adherence is likely to have greater benefits in this group than any novel treatment (16). Despite the fact, there is hardly any evidence on adherence to asthma medication and its influencing factors among patients of Bangladesh. Moreover, using non-validated or generalized tool for adherence assessment may invariably underestimate the incidence of non-adherence rates to the inhalers among asthma patients (8). Hence, the present study aimed to

to assess self-reported adherence level and to identify the potential factors associated with non-adherence to the inhalers among asthma patients.

Methods

Study design and participants

This facility-based cross-sectional study was conducted in the medicine outpatient department of Rajshahi Medical College Hospital, a tertiary care referral hospital from November 2020 to January 2021. All the adult patients (aged ≥ 18 years) visiting the department with the diagnosis of asthma

were the study population. Sample size was calculated from the following formula: $n = \frac{z^2 p(1-p)}{d^2}$, where, z = 1.96 for 95% confidence level, p = assumed prevalence of poor adherence to inhaler therapy, d = allowable error of assumed prevalence. Due to lack of existing evidence, we assumed the prevalence of adherence to inhaler therapy as 50% among the asthma patients of Bangladesh and the calculated sample size was 384. Assuming 5% non-response rate we approached a total of 400 patients. Patients aged ≥ 18 years, had diagnosed asthma and were using at least one metered dose inhaler (MDI) with or without spacer and/or dry powder inhaler (DPI) for at least one year were included in the study. Patients having asthma-COPD overlap syndrome, other obstructive lung disease, chronic debilitating conditions (e.g. carcinoma), women with pregnancy and using inhaler for less than one year were excluded. The consecutive eligible patients during the study period were recruited until the targeted number of patients was reached. After excluding the incomplete data 357 patients were included in the final analysis.

Data Collection

Face-to-face interview by five trained physicians after the consultation using a structured questionnaire and check lists was conducted to collect data from the patients and their medical record respectively. The questionnaire had four parts: (i) socio-demographic characteristics of the patients, (ii) information of inhalers they used and measurement of inhaler adherence, (iii) a demonstration session of their inhaler using technique to identify any critical error, and (iv) asthma control status using the Asthma Control Test (ACT) The questionnaire was prepared in English and translated to Bangla. Back translated version was compared with original version to confirmed the equivalence across the language. A consortium was made to check the consistency of the translation and was pretested among 20 asthma patients before using it.

The 10-item Test of Adherence scale (TAI) based on a five-point Likert scale, which was developed and validated by Plaza et. al. (17) and widely used in different countries (18,19) were used to assess the inhaler adherence of asthma patients. However, the scale was not previously used among Bangladeshi patients, hence it was not previously validated. Patients are considered as good, intermediate and poor adherent if they score 50, 46-49 and ≤ 45 respectively (17,18). In our study, poor adherence (TAI score ≤ 45) was considered as non-adherent.

Patients were requested to demonstrate their inhaler using technique and were scored in a checklist adapted from a previous study based on the recommendation of the American Thoracic Society according to the steps completed by the patients to identify any critical error (2).

Outcome and independent variables

Non-adherence to inhaler among asthma patients (TAI score ≤ 45) was the outcome variable of the present study. Independent variables were sociodemographic characteristics of the patients (age, sex, residence, educational status, family income etc.), disease profile (smoking history, comorbidity, health seeking behavior), and inhaler related information (type, number and duration of inhaler usage, perceived difficulty and critical error of inhaler using technique, and self-reported efficacy of inhaler).

Statistical analyses

All the statistical analyses were made by using STATA version 16.0. Both univariable and multivariable logistic regression models adjusted for socio-demographic and inhaler related factors were used to determine the predictors of poor adherence to inhaler of the asthma patients. The variance inflation factor (VIF) was used to detect any evidence of multicollinearity problem among independent variables. Statistical significance level was set at p-value < 0.05 for 95% confidence interval (CI).

Ethical consideration

Ethical approval was obtained from the ethical review committee of Rajshahi Medical College to conduct the study; Memo no: RMC/IRB/2020-2021/121. Informed written consent was also obtained from each respondent after explaining the purpose of the study.

Results

Characteristics of the participants

A total of 357 asthma patients were included in the study. Their mean (SD) age was 34.5 (10.2) years. Almost two-thirds of the participants were female (65%) and hailing from rural areas (62%). Almost half of them attended up to secondary level of education and from low income families. MDI was the most commonly used inhaler device by the patients (75% without spacer and 13% with spacer) followed by DPI (12%). In accounts of inhaler using duration, almost 20% were using inhaler for less than one year, 47% for 2 to 5 years, and 33% for more than 5 years. Almost half of them preferred non-qualified practitioners for their regular respiratory problems (Table 1).

Adherence to inhaler

The Cronbach's Alpha of the TAI scale was 0.87. Mean (SD) TAI score of the asthma patients was 36.5 (7.9). Majority of the patients (86%) reported poor adherence to their inhalation therapy (TAI score ≤ 45). Almost 8% of them reported good adherence (TAI score 50) and 6% showed moderate adherence (TAI score 46-49) (Table 1). Responses to each questions of TAI scale by the asthma patients are demonstrated in Table 2.

Table 1: Sociodemographic characteristics and inhaler adherence (n = 357)

Characteristics	N	%
Age (years) (mean = 34.54, SD = 10.18)		
18-30	148	41.46
31-40	124	34.73
>40	85	23.81
Sex		
Male	232	64.99
Female	125	35.01
Residence		
Rural	135	37.82
Urban	222	62.18
Schooling year		
≤5	68	19.05
6-10	119	33.33
>10	170	47.62
Family income		
Low	196	54.90
Middle	138	38.66
High	23	6.44
Smoking		
Yes	55	15.41
No	302	84.59
Comorbidity		
DM	28	7.84
HTN	41	11.48
CAD	19	5.32
Others	3	0.84
Number of inhaler		
Single	284	79.55
Multiple	73	20.45
Device		
MDI only	270	75.63
MDI + Spacer	46	12.89
DPI	41	11.48
Duration of inhaler usage (years)		
≤5	241	67.51
>5	116	32.49
Primary care seeking behavior		
Non-qualified practitioner	166	46.50
Qualified physician	191	53.50
Demonstration of inhaler using technique		

No	127	35.57
Yes	230	64.43
Difficulty of using inhaler		
Very difficult	28	7.84
Somewhat difficult	178	49.86
Easy	151	42.30
Self-reported efficacy of inhaler		
Not effective	21	5.88
Somewhat effective	158	44.26
Effective	178	49.86
Hospital admission due to respiratory problem during last 12 months		
Yes	79	22.13
No	278	77.87
Critical error		
Yes	279	78.15
No	78	21.85
Inhaler adherence		
Overall TAI score	Mean = 36.45	SD = 7.93
Good adherence	27	7.6
Moderate adherence	21	5.9
Poor adherence	309	86.5

Table 2: Responses to the TAI questions by the asthma patients (n = 357)

TAI questions	Responses				
	All n (%)	More than half n (%)	About half n (%)	Less than half n (%)	None n (%)
How many times did you forget to take your regular inhalers in the last 7 days?	99 (27.73)	99 (27.73)	115 (32.21)	40 (11.20)	4 (1.12)
You forget to take your inhalers	86 (24.09)	87 (24.37)	75 (21.01)	101 (28.29)	8 (2.24)
	Always n (%)	Almost always n (%)	Sometimes n (%)	Almost never n (%)	Never n (%)
When you are feeling well, you stop taking your inhalers	67 (18.77)	59 (16.53)	80 (22.41)	102 (28.57)	49 (13.73)
At the weekend or when you go on holiday, you stop taking your inhalers	93 (26.05)	70 (19.61)	69 (19.33)	96 (26.89)	29 (8.12)
When you are anxious or sad, you stop taking your inhalers	134 (37.54)	108 (30.25)	60 (16.81)	35 (9.80)	20 (5.60)
You don't take your inhalers out of fear of potential side effects	177 (49.58)	116 (32.49)	37 (10.36)	23 (6.44)	4 (1.12)
You stop taking your inhalers because you believe that they are of little help in treating your disease	196 (54.90)	82 (22.97)	47 (13.17)	30 (8.40)	2 (0.56)
You take fewer inhalations than prescribed by your doctor	85 (23.81)	53 (14.85)	100 (28.01)	99 (27.73)	20 (5.60)
You stop taking your inhalers because you believe that they interfere with your day-to-day or work life	160 (44.82)	81 (22.69)	65 (18.21)	47 (13.17)	4 (1.12)
You stop taking your inhalers because you have trouble paying for them	129 (36.13)	56 (15.69)	88 (24.65)	63 (17.65)	21 (5.88)

Predictors of non-adherence to inhalers

Multivariable logistic regression models demonstrated that younger people were more chance to be non-adherent to their inhaler therapy (aOR 23.15, 95% CI 3.67-146.08 for patients aged from 18 to 30 and aOR 8.72, 95% CI 1.62-46.85 for patients aged from 31 to 40). Besides, rural residence, less schooling year and middle income were identified as significant predictors of non-adherence to inhaler (aOR 23.28, 95% CI 2.43-222.66 for rural residence, aOR 5.69, 95% CI 1.27-25.44 for schooling year ≤ 5 years and aOR 9.74, 95% CI 2.11-44.93 for middle income). Patients having comorbidities and using inhaler for a longer period were more likely to be non-adherent to their therapy (aOR 12.91, 95% CI 1.41-117.61 for having comorbidities and aOR 5.69, 95% CI 1.22-26.49 for using inhaler >5 years). Finally, patients visiting non-qualified practitioners (such as quacks, drug sellers etc.) for their regular physical problems and reported inhaler using technique as difficult had a higher chance of non-adherence ((aOR 13.09, 95% CI 3.10-55.26 and aOR 10.56, 95% CI 2.95-37.73 respectively) (Table 3).

Table 3: Factors associated with non-adherence to inhalers among asthma patients (univariable and multivariable logistic regression models)

Variables	Non-adherence		cOR (95% CI)	aOR (95% CI)
	Yes	No		
Age (years)				
18-30	140 (94.59)	8 (5.41)	5.03 (2.09-12.10)*	23.15 (3.67-146.08)*
31-40	103 (83.06)	21 (16.94)	1.41 (0.70-2.82)	8.72 (1.62-46.85)*
>40	66 (77.65)	19 (22.35)	1	1
Sex				
Male	206 (88.79)	26 (11.21)	1.69 (0.91-3.13)	1.06 (0.28-3.96)
Female	103 (82.40)	22 (17.60)	1	1
Residence				
Rural	131 (97.04)	4 (2.96)	8.09 (2.83-23.09)*	23.28 (2.43-222.66)*
Urban	178 (80.18)	44 (19.82)	1	1
Schooling year				
≤5	62 (91.18)	6 (8.82)	1.69 (0.66-4.36)	5.69 (1.27-25.44)*
6-10	101 (84.87)	18 (15.13)	0.92 (0.47-1.78)	2.76 (0.69-11.08)
>10	146 (85.88)	24 (14.12)	1	1
Family income				
Low	155 (79.08)	41 (20.92)	1	1
Middle	134 (97.10)	4 (2.90)	8.86 (3.0925.38)*	9.74 (2.11-44.93)*
High	20 (86.96)	3 (13.04)	1.76 (0.50-6.22)	3.57 (0.17-74.68)
Smoking				
Yes	43 (78.18)	12 (21.82)	0.48 (0.23-1.01)	0.51 (0.10-2.61)
No	266 (88.08)	36 (11.92)	1	1
Comorbidity				
Yes	42 (84.00)	8 (16.00)	0.78 (0.34-1.79)	12.91 (1.41-117.61)*
No	267 (86.97)	40 (13.03)	1	1
Number of inhaler				
Single	251 (88.38)	33 (11.62)	1.96 (1.01-3.85)*	0.92 (0.26-3.24)
Multiple	58 (79.45)	15 (20.55)	1	1
Device				
MDI only	233 (86.30)	37 (13.70)	1.52 (0.65-3.56)	0.56 (0.14-2.22)
MDI + Spacer	43 (93.48)	3 (6.52)	3.47 (0.85-14.12)	2.81 (0.11-68.68)
DPI	33 (80.49)	8 (19.51)	1	1
Duration of inhaler usage (years)				
≤5	197 (81.74)	44 (18.26)	1	1
>5	112 (96.55)	4 (3.45)	6.25 (2.19-17.86)*	5.69 (1.22-26.49)*
Primary care seeking behavior				
Non-qualified practitioner	160 (96.39)	6 (3.61)	7.51 (3.11-18.19)*	13.09 (3.10-55.26)*
Qualified physician	149 (78.01)	42 (21.99)	1	1
Demonstration of inhaler using technique				
No	117 (92.13)	10 (7.87)	2.31 (1.11-4.82)*	1.32 (0.32-5.39)

Yes	192 (83.48)	38 (16.52)	1	1
Difficulty of using inhaler				
Very difficult	26 (92.86)	2 (7.14)	4.22 (0.95-18.63)	5.56 (0.73-42.27)
Somewhat difficult	169 (94.94)	9 (5.06)	6.09 (2.83-13.11)*	10.56 (2.95-37.73)*
Easy	114 (75.50)	37 (24.50)	1	1
Self-reported efficacy of inhaler				
Effective	154 (86.52)	24 (13.48)	1.51 (0.46-4.87)	2.64 (0.36-19.51)
Somewhat effective	138 (87.34)	20 (12.66)	1.62 (0.49-5.31)	2.79 (0.35-22.36)
Not effective	17 (80.95)	4 (19.05)	1	1
Critical error				
Yes	256 (91.76)	23 (8.24)	5.25 (2.77-9.94)*	1.49 (0.45-5.00)
No	53 (67.95)	25 (32.05)	1	1

*p-value <0.05

Discussion

Adherence to the inhaler and correct using technique of the device is crucial for asthma control. Our study provides a birds' eye view on the non-adherence to inhaler medication among the adult asthma patients of Bangladesh which exceeds 86%. Existing evidence on this issue is scarce from this country to compare with. However, some recent studies from neighboring India reported the rate of poor adherence to inhalation therapy as 71% among adult and 55% among pediatric asthma patients (20,21). Another study from some developing countries of Africa, like Ethiopia and Egypt reported that almost half of the asthma patients were non-adherent to their medication (8,22). Though, these adherence rates were also suboptimal, situation was quite better compared to ours. However, we used self-reported 'Test of Adherence to Inhaler' scale, which was a subjective assessment and might overestimate the non-adherence. The TAI test yielded high rates of poor adherence even in developed countries. For example, the ASCONA study conducted among the asthma patients of Europe reported that almost 60% patients were poor adherent to their prescribed therapy (23). A recent study reported almost 58% poor inhaler adherence rate using the 'TAI' scale, while the rate was 29% using the pharmacy refill records, which was a more objective scale (24). However, another study from Denmark suggested that self-reported measurements overestimates the adherence rate and might not be used as a reliable indicator (25).

A number of personal and socioeconomic factors are reported to influence the inhaler adherence among the asthma patients. In our study, younger people were more likely to be non-adherent irrespective of their gender. Similar phenomenon was observed in a recent meta-analysis which reported that female and younger patients are more like to be non-adherent to their inhaler therapy (13). In our study, the rural patients belonged to middle income families and those who were using their inhalers for a longer period of time had comparatively lower adherence rate than the urban patients. In contrast to our findings, a large-scale multi-country study from European asthma patients reported no such association of these factors with inhaler adherence (12). Though some studies suggested that patients using DPI device had a better adherence to their inhalers (26,27), our finding did not support that. However, a very small number of patients of our study were using DPI to conclude. Besides, patients who visited non-qualified practitioners for their regular respiratory problems had more chance to be non-adherent to their therapies. Similar finding was reported by a study among inhaler using COPD patients that reported that patients who received primary care from feedback from non-qualified care providers were less sustained in medication adherence (28). Some studies including ours reported that having comorbidity may cause medication non-adherence among asthma patients (29,30). Medication burden and increased cost may be the underlying factor of this finding. Besides these, patients' belief and perception about the disease and its severity, self-care ability, family and social support, communication quality with healthcare providers as well as perceived efficacy of the therapy was reported as influencing factor for inhaler adherence in several studies (10,11,13,31–34). These factors were not explored extensively in our study. However, patients who reported inhaler using technique as difficult had a higher chance of non-adherence. Further qualitative studies addressing the patients' behavioral factors and perceived barriers for inhaler adherence is necessary for better understanding. Multidisciplinary approach to support the patient both mentally and physically, shared decision making between provider and patients based on possible risk and benefits could better the inhaler adherence.

The ASCONA study conducted among a large European asthma cohort reported that patients having good adherence to their inhaler therapies had a better asthma control irrespective of age, sex, comorbidity and treatment modality (23). Another large scale cohort study reported that asthma patients maintaining high adherence to their inhalers over time, had a better control of asthma (35). Moreover, a recent review of published articles on this topic reported that good adherence to inhalers decreased the number and frequency of severe asthma exacerbations in high-quality studies (36). Based on these evidence, it may be concluded that adherence to inhalers is a major contributor of asthma control.

Limitations

Our study had several limitations. Firstly, it was conducted among the patients of asthma who visited hospital outdoor for their exacerbation or other issues and so, the findings could not be inferential for the overall patient population from the community. Moreover, we used a self-reported adherence measuring tool that could potentially underestimate the non-adherence rate to inhalers as social desirability bias could not be rolled out. Finally detailed exploration of the perceived barriers of the patients was not explored extensively.

Conclusions

Despite being an important contributing factor to asthma control, adherence rate to the inhalers was poor among our patients. Regular investigation for patients' adherence to the prescribed inhalers is necessary for patients with uncontrolled asthma. Adequate patient education and counselling about the nature of disease and importance of regular use of inhalers as well as encouraging patients to seek treatment from qualified physicians is suggested to improve the inhaler adherence.

Abbreviations

GINA: Global Initiative for Asthma, MDI: Metered dose inhaler, DPI: Dry powder inhaler, ACT: Asthma Control Test, TAI: Test of Adherence scale, CI: Confidence interval

Declarations

Funding

The authors did not receive any fund to report.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MAR, KA, MJH, MAH, MGH contributed to the study conception and design, data analysis and interpretation. MAR, CIT, TS, MJH, MAH contributed to drafting the manuscript. CIT, ST, ASB, FJ, SJM, ABS, SS, AR, MM, NN, TS, ARM contributed to the data acquisition, data interpretation and critical revision of the manuscript for important intellectual content. All authors approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the ethical review committee of Rajshahi Medical College to conduct the study; Memo no: RMC/IRB/2020-2021/121. Informed written consent was also obtained from each respondent after explaining the purpose of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Horak F, Doberer D, Eber E, Horak E, Pohl W, Riedler J, et al. Diagnosis and management of asthma – Statement on the 2015 GINA Guidelines. Wiener Klin Wochenschrift 2016 12815 [Internet]. 2016 Jul 1 [cited 2021 Jul 9];128(15):541–54. Available from: <https://link.springer.com/article/10.1007/s00508-016-1019-4>
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J [Internet]. 2008 Jan 1 [cited 2021 Oct 22];31(1):143–78. Available from: <https://erj.ersjournals.com/content/31/1/143>
3. Global Asthma Network. The Global Asthma report (2018) [Internet]. 2018 [cited 2021 Jul 9]. Available from: https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Global+Asthma+Network.+%282018%29.+the+Global+Asthma+Report+2018.+In+Auckland%2C+New+Zealand&btnG=
4. Braman SS. The Global Burden of Asthma. Chest [Internet]. 2006 Jul 1 [cited 2021 Oct 22];130(1):4S-12S. Available from: <http://journal.chestnet.org/article/S0012369215329524/fulltext>

5. Bishwajit G, Tang S, Yaya S, Feng Z. Burden of asthma, dyspnea, and chronic cough in South Asia. *Int J Chron Obstruct Pulmon Dis* [Internet]. 2017 Apr 6 [cited 2021 Jul 9];12:1093. Available from: [/pmc/articles/PMC5388281/](https://pubmed.ncbi.nlm.nih.gov/271093/)
6. Borghardt JM, Kloft C, Sharma A. Inhaled Therapy in Respiratory Disease: The Complex Interplay of Pulmonary Kinetic Processes. *Can Respir J* [Internet]. 2018 Jun 19 [cited 2021 Jul 9];2018. Available from: [/pmc/articles/PMC6029458/](https://pubmed.ncbi.nlm.nih.gov/3029458/)
7. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma (GINA) Strategy 2021 - Executive summary and rationale for key changes. *Eur Respir J* [Internet]. 2021 Oct 19 [cited 2021 Oct 22];2102730. Available from: <https://erj.ersjournals.com/content/early/2021/10/14/13993003.02730-2021>
8. Ayele AA, Tegegn HG. Non adherence to inhalational medications and associated factors among patients with asthma in a referral hospital in Ethiopia, using validated tool TAI. *Asthma Res Pract* 2017 31 [Internet]. 2017 Oct 6 [cited 2021 Jul 15];3(1):1–6. Available from: <https://link.springer.com/articles/10.1186/s40733-017-0035-0>
9. Heaney LG, Horne R. Non-adherence in difficult asthma: time to take it seriously. *Thorax* [Internet]. 2012 Mar 1 [cited 2021 Jul 30];67(3):268–70. Available from: <https://thorax.bmj.com/content/67/3/268>
10. Gamble J, Stevenson M, Heaney LG. A study of a multi-level intervention to improve non-adherence in difficult to control asthma. *Respir Med* [Internet]. 2011 Sep 1 [cited 2021 Jul 30];105(9):1308–15. Available from: <http://www.resmedjournal.com/article/S0954611111001090/fulltext>
11. Gamble J, Stevenson M, McClean E, Heaney LG. The Prevalence of Nonadherence in Difficult Asthma. <https://doi.org/10.1164/rccm.200902-0166OC> [Internet]. 2012 Dec 20 [cited 2021 Jul 30];180(9):817–22. Available from: www.atsjournals.org
12. Corsico AG, Cazzoletti L, Marco R de, Janson C, Jarvis D, Zoia MC, et al. Factors affecting adherence to asthma treatment in an international cohort of young and middle-aged adults. *Respir Med* [Internet]. 2007 Jun 1 [cited 2021 Jul 30];101(6):1363–7. Available from: <http://www.resmedjournal.com/article/S0954611106005993/fulltext>
13. Hassan M, Davies SE, Trethewey SP, Mansur AH. Prevalence and predictors of adherence to controller therapy in adult patients with severe/difficult-to-treat asthma: a systematic review and meta-analysis. <https://doi.org/10.1080/0277090320191645169> [Internet]. 2019 [cited 2021 Jul 30];57(12):1379–88. Available from: <https://www.tandfonline.com/doi/abs/10.1080/02770903.2019.1645169>
14. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: A review of the prevalence, disease burden and options for treatment. *Respir Med*. 2006 Jul 1;100(7):1139–51.
15. Chen S, Golam S, Myers J, Bly C, Smolen H, Xu X. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA Steps 4 or 5 treatment. <https://doi.org/10.1080/0300799520181505352> [Internet]. 2018 Dec 2 [cited 2021 Jul 10];34(12):2075–88. Available from: <https://www.tandfonline.com/doi/abs/10.1080/03007995.2018.1505352>
16. Lindsay JT, Heaney LG. Nonadherence in difficult asthma – facts, myths, and a time to act. *Patient Prefer Adherence* [Internet]. 2013 Apr 19 [cited 2021 Oct 22];7:329–36. Available from: <https://www.dovepress.com/nonadherence-in-difficult-asthma-ndash-facts-myths-and-a-time-to-act-peer-reviewed-fulltext-article-PPA>
17. Plaza V, Fernández-Rodríguez C, Melero C, Cosío BG, Entrenas LM, De Llano LP, et al. Validation of the “Test of the Adherence to Inhalers” (TAI) for Asthma and COPD Patients. *J Aerosol Med Pulm Drug Deliv* [Internet]. 2016 Apr 1 [cited 2021 May 23];29(2):142–52. Available from: <https://pubmed.ncbi.nlm.nih.gov/26230150/>
18. Montes De Oca M, Menezes A, Wehrmeister FC, Lopez Varela MV, Casas A, Ugalde L, et al. Adherence to inhaled therapies of COPD patients from seven Latin American countries: The LASSYC study. *PLoS One* [Internet]. 2017 Nov 1 [cited 2021 May 23];12(11):e0186777. Available from: <https://doi.org/10.1371/journal.pone.0186777>
19. Muneswarao J, Hassali MA, Ibrahim B, Saini B, Naqvi AA, Ali IAH, et al. Translation and validation of the Test of Adherence to Inhalers (TAI) questionnaire among adult patients with asthma in Malaysia. <https://doi.org/10.1080/0277090320201776728> [Internet]. 2020 [cited 2021 Jul 15]; Available from: <https://www.tandfonline.com/doi/abs/10.1080/02770903.2020.1776728>
20. Santhakumar S. Assessment of adherence to inhalers in asthmatics. *Pulmon* [Internet]. 2021 Apr 30 [cited 2021 Jul 15];23(1):7–7. Available from: <https://www.pulmon.in/index.php/pulmon/article/view/10>
21. Sinha R, Lahiry S, Ghosh S. Suboptimal compliance to aerosol therapy in pediatric asthma: A prospective cohort study from Eastern India. *Lung India* [Internet]. 2019 [cited 2021 Jul 15];36(6):512. Available from: [/pmc/articles/PMC6852208/](https://pubmed.ncbi.nlm.nih.gov/36852208/)
22. Ali AHK, Ameen E, Atta K, Alkhayat KF. Drug-related factors affecting medication adherence among Egyptian asthma patients. *Egypt J Bronchol* 2020 141 [Internet]. 2020 Oct 20 [cited 2021 Jul 15];14(1):1–7. Available from: <https://ejb.springeropen.com/articles/10.1186/s43168-020-00035-w>
23. Pereyra FG, Plaza V, Bustamante V, Calle M, Contreras FJ, Giner J, et al. Control of asthma, adherence to inhaled therapy and usefulness of the Test of Adherence to Inhalers (TAI). Results of the ASCONA study. *Eur Respir J* [Internet]. 2017 Sep 1 [cited 2021 Jul 15];50(suppl 61):PA534. Available from: https://erj.ersjournals.com/content/50/suppl_61/PA534
24. Plaza V, Giner J, Curto E, Alonso-Ortiz MB, Orue MI, Vega JM, et al. Assessing adherence by combining the test of adherence to inhalers with pharmacy refill records. *J Investig Allergol Clin Immunol* [Internet]. 2021 Oct 10 [cited 2021 May 23];31(1):58–64. Available from: <https://europepmc.org/article/med/31599726>

25. Jensen FF, Håkansson KEJ, Overgaard Nielsen B, Weinreich UM, Ulrik CS. Self-reported vs. objectively assessed adherence to inhaled corticosteroids in asthma. *Asthma Res Pract* 2021 71 [Internet]. 2021 May 31 [cited 2021 Jul 30];7(1):1–9. Available from: <https://asthmarp.biomedcentral.com/articles/10.1186/s40733-021-00072-2>
26. 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 202 [Internet]. 2011 Mar 24 [cited 2021 Jul 30];20(2):148–54. Available from: <https://www.nature.com/articles/pcrj201122>
27. Crompton GK. How to achieve good compliance with inhaled asthma therapy. *Respir Med*. 2004 Oct 1;98(SUPPL. 2):S35–40.
28. Humenberger M, Horner A, Labek A, Kaiser B, Frechinger R, Brock C, et al. Adherence to inhaled therapy and its impact on chronic obstructive pulmonary disease (COPD). *BMC Pulm Med* 2018 181 [Internet]. 2018 Oct 19 [cited 2021 Jul 30];18(1):1–6. Available from: <https://bmcpulmed.biomedcentral.com/articles/10.1186/s12890-018-0724-3>
29. Kebede B, Mamo G. Determinants of non-adherence to inhaled steroids in adult asthmatic patients on follow up in referral hospital, Ethiopia: cross-sectional study. *Asthma Res Pract* 2019 51 [Internet]. 2019 Dec 30 [cited 2021 Jul 30];5(1):1–8. Available from: <https://asthmarp.biomedcentral.com/articles/10.1186/s40733-019-0053-1>
30. Ayele AA, Tegegn HG. Non adherence to inhalational medications and associated factors among patients with asthma in a referral hospital in Ethiopia, using validated tool TAI. *Asthma Res Pract* 2017 31 [Internet]. 2017 Oct 6 [cited 2021 Jul 30];3(1):1–6. Available from: <https://asthmarp.biomedcentral.com/articles/10.1186/s40733-017-0035-0>
31. Vrijens B, Dima AL, Van Ganse E, van Boven JFM, Eakin MN, Foster JM, et al. What We Mean When We Talk About Adherence in Respiratory Medicine. *J Allergy Clin Immunol Pract*. 2016 Sep 1;4(5):802–12.
32. Amin S, Soliman M, Mclvor A, Cave A, Cabrera C. <p>Understanding Patient Perspectives on Medication Adherence in Asthma: A Targeted Review of Qualitative Studies</p>. *Patient Prefer Adherence* [Internet]. 2020 Mar 10 [cited 2021 Jul 30];14:541–51. Available from: <https://www.dovepress.com/understanding-patient-perspectives-on-medication-adherence-in-asthma-a-peer-reviewed-fulltext-article-PPA>
33. Dima AL, Hernandez G, Cunillera O, Ferrer M, Bruin M de, group the A-L. Asthma inhaler adherence determinants in adults: systematic review of observational data. *Eur Respir J* [Internet]. 2015 Apr 1 [cited 2021 Jul 30];45(4):994–1018. Available from: <https://erj.ersjournals.com/content/45/4/994>
34. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am*. 2005 Feb 1;25(1):107–30.
35. Dima AL, Ganse E van, Stadler G, Bruin M de. Does adherence to inhaled corticosteroids predict asthma-related outcomes over time? A cohort study. *Eur Respir J* [Internet]. 2019 Dec 1 [cited 2021 Jul 30];54(6):1900901. Available from: <https://erj.ersjournals.com/content/54/6/1900901>
36. Engelkes M, Janssens HM, Jongste JC de, Sturkenboom MCJM, Verhamme KMC. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* [Internet]. 2015 Feb 1 [cited 2021 Jul 30];45(2):396–407. Available from: <https://erj.ersjournals.com/content/45/2/396>