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CARE: an observational study of adherence to home nebulizer therapy among children with asthma

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Abstract

Background: The prevalence of pediatric asthma in China is approximately 3%, and asthma remains poorly controlled in many of these patients. This study assessed the rate of adherence to home nebulizer treatment in paediatric patients in China.

Methods: The CARE study was a 12-week, multicentre, prospective, observational study across 12 tertiary hospitals in China. Patients were aged 0–14 years, clinically diagnosed with asthma and prescribed home nebulizer inhaled corticosteroid (ICS) therapy for ⩾3 months. The primary endpoint was electronically monitored treatment adherence. Patients attended onsite visits at 0, 4, 8 and 12 weeks to assess asthma control, severity and treatment adherence (recorded by electronic monitoring devices and caregivers).

Results: The full analysis set included 510 patients. Median treatment adherence reported by electronic monitoring devices was 69.9%, and median caregiver-reported adherence was 77.9%. The proportion of patients with well-controlled asthma increased from 12.0% at baseline to 77.5% at visit 4. Increased time between asthma diagnosis and study enrolment was a significant predictor for better adherence [coefficient: 0.01, $p = 0.0138$; 95% confidence interval (CI): 0.00, 0.01] and asthma control (odds ratio = 1.001, $p = 0.0498$; 95% CI: 1.000, 1.002). Negative attitude to treatment by the caregiver was associated with poorer asthma control.

Conclusions: Adherence to home nebulization, a widely used treatment for asthma, was high among Chinese pediatric patients. Asthma control improved with increasing treatment duration. These results suggest that home nebulization of ICS is an effective and recommendable long-term treatment for paediatric patients with asthma.

Trial registration

ClinicalTrials.gov identifier: NCT03156998

The reviews of this paper are available via the supplemental material section.

Keywords: asthma, nebulizers and vaporizers, treatment adherence and compliance

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Introduction

In China, the prevalence of paediatric asthma has increased over the past 20 years and is now approximately 3%.[1,2] The long-term goals of asthma management according to the Global Initiative for Asthma (GINA) 2020 update are to improve and individualize the care of patients with asthma so that patients are able to achieve good control of symptoms and maintain normal activity levels, and have minimized risk of: asthma-related death, exacerbations, persistent airflow limitation and side effects.[3] The 2020 GINA guidelines suggest that poor adherence can be identified in clinical practice by empathic questioning that encourages open discussion, and acknowledges the probability of incomplete adherence.[3] For optimal control of chronic diseases such as asthma, long-term adherence to

treatment is required. If symptom control is poor and/or exacerbations persist despite 3 months of controller therapy, before considering a step-up of controller treatment, the relationship of symptoms to asthma should be confirmed, inhaler technique checked, good adherence confirmed or for children under 5-years old, an alternative treatment considered.[3]

There are several methods of collecting treatment adherence information from patients, but commonly, this information is obtained from patient/caregiver treatment diaries. However, children and adolescents with asthma have been found to overestimate their level of adherence.[4–6] The gold standard method for measuring treatment adherence is an electronic monitoring device that digitally records the frequency of treatment administration.[7,8]

Real-world data on adherence to asthma medication in the paediatric population in China are limited. There are currently no published real-world data on adherence to home nebulization of inhaled corticosteroid (ICS) treatment in Chinese asthmatic children monitored by electronic devices or on the difference between adherence measured by electronic monitoring devices and that reported by caregivers. This multicentre, prospective, observational study aimed to assess treatment adherence in paediatric patients diagnosed with asthma and prescribed home nebulizer therapy.

Methods

Study design

The CARE study [ClinicalTrials.gov identifier: NCT03156998] was a multicentre, prospective, observational study across 12 tertiary hospitals in China. Subjects were consecutively enrolled and asthma medication was prescribed as per routine clinical practice. A portable nebulizer device POCKET AIR® MBPN002 (Microbase Technology Corp, Taiwan) for home use was supplied by the investigators for the study duration. An electronic chip was embedded into the device to record duration and frequency of nebulizer use. Subjects were informed about the purpose, procedures, risk, and benefits of the study. Treatment adherence was recorded by the electronic chip, and patients/caregivers were asked to accurately record symptoms and medication use every day, using a diary card. Any incomplete or missing records were checked with the patients and completed to the extent possible during clinic visits.

The primary endpoint was electronically monitored treatment adherence, derived by dividing the actual treatment frequency by the prescribed frequency. One eligible use was defined as the use of nebulizer therapy for at least 5 min (cumulative) in a 30-minute period; if the prescription was twice a day, the interval between two eligible uses needed to be >4 h. Data were downloaded from the electronic monitoring devices at every onsite visit. The secondary endpoints were to find out:

(1) treatment adherence reported by caregivers, derived by dividing the actual dose (recorded in diary) by the prescribed dose;
(2) proportion of patients in different treatment adherence levels, reported by electronic monitoring devices and caregivers;
(3) asthma severity according to GINA 2016;[9]
(4) mild asthma: well controlled with step 1 or 2, for example, with reliever medication as needed or with low-intensity controller treatment such as low-dose ICS, leukotriene receptor antagonist or chromones;
(5) moderate asthma: well controlled with step 3 treatment [e.g. low-dose ICS/long-acting beta agonist (LABA)];
(6) severe asthma: requires a step 4 or 5 treatment (e.g. high-dose ICS/LABA) to prevent the asthma becoming uncontrolled, despite treatment;
(7) asthma control status according to GINA 2016:[9]
    (a) daytime asthma symptoms more than twice/week;
    (b) night-time waking due to asthma;
    (c) symptoms requiring use of reliever more than twice/week;
    (d) activity limitation due to asthma;
    (e) risk factors for poor outcomes and exacerbations;
    (f) risk factors for developing fixed airflow limitation;
    (g) risk factors for medication side effects;
(8) factors associated with treatment adherence and asthma control.

Ethical statement and clinical trial registration

The study has been approved by the ethics committees of participating study centres. Signed and dated consent was obtained from patients,

patients' parents or guardians for all participants. The study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice and Good Publication Practice guidelines, and the applicable legislation on non-interventional studies and observational studies.

Patients

Patients aged 0–14 years were eligible for study enrolment if they were clinically diagnosed with asthma according to Chinese paediatric asthma diagnosis and treatment guidelines[2,10] and all had previously been prescribed home nebulizer ICS therapy for ⩾3 months, prior to enrolment. The age range selected reflects the range used in other key studies (e.g. an epidemiological survey of asthma in children)[11] and historical clinical practice of children's hospitals treating patients up to 14 years old, which has not changed rapidly despite being expanded to 18-years old more recently. Only those with a definitive diagnosis of asthma, according to the specified guidelines, were included. Paediatric asthma diagnosis was fulfilled when patients exhibited criteria one to four or criteria four and any of those in five:

(1) Recurrent respiratory symptoms (wheeze, cough, dyspnoea, chest tightness) that were typically worse at night/early morning and exacerbated by exercise, viral infection, allergens, smoke, dust, pets, mould, dampness, weather changes, laughing or crying.
(2) A high-pitched whistling sound could be detected in both sides of the lung by auscultation of the chest. The wheezing is usually during exhalation.
(3) The signs and symptoms described above could be relieved automatically or by anti-asthmatic treatment.
(4) Other diseases that could cause wheezing, cough, dyspnoea or chest tightness have been excluded.
(5) Atypical symptoms without wheezing or whistling sounds: positive bronchial provocation test; reversible airflow limitation when the bronchial dilation test is positive or when anti-asthmatic treatment is effective for lung function improvement; or if the ration of daily variation in peak expiratory flow is ⩾13% for ⩾2 consecutive weeks.

Patients were ineligible for enrolment if they had an allergy to ICS, presented with other diseases/conditions (including other pulmonary conditions, differential diagnosis of asthma such as congenital heart disease, gastro-oesophageal reflux, bronchopulmonary dysplasia or bronchiolitis obliterans) that may have interfered with the study results as judged by the investigator, were participating in another ongoing clinical study, or had a parent/caregiver that was not proficient in expressing, understanding, writing and reading in Chinese (judged by the investigator).

Assessments

The study comprised four onsite visits at 0, 4, 8 and 12 weeks. At visit 1 (baseline), informed consent and medical history were obtained, GINA 2016 asthma control status[9] and lung function were assessed, and caregivers' knowledge of asthma was collected by questionnaire (Supplemental Material: Paediatric asthma knowledge questionnaire of parents). At visits 2–4, GINA 2016 asthma control status,[9] and exacerbation and treatment adherence information were collected. Lung function data were collected at each visit if tests were performed as per clinical practice. Asthma severity was assessed at visit 1 and visit 4, according to GINA 2016: mild asthma is asthma that can be well controlled with step 1 or step 2 treatment (i.e. with as-needed reliever medication alone, or with low-intensity controller treatment such as low-dose ICS, leukotriene receptor antagonist or chromones); moderate asthma is asthma that can be well controlled with step 3 treatment (e.g. low-dose ICS/LABA); severe asthma is asthma that requires a step 4 or 5 treatment (e.g. high-dose ICS/LABA) to maintain symptom control. Daily and on-demand medications were recorded in an asthma diary by the caregiver.

Statistical analysis

The statistical analysis was primarily descriptive in nature based on the full analysis set (FAS). The FAS included all enrolled patients who fulfilled the inclusion/exclusion criteria. Sensitivity analyses were performed based on the per protocol set (PPS), which included patients having received the treatment and no major protocol deviations with baseline data, and at least one post-baseline record available. Patients who withdrew informed consent during the study still met inclusion criteria for both FAS and PPS, as per protocols, and were included in both FAS and PPS analyses. Factors influencing adherence to medication and asthma

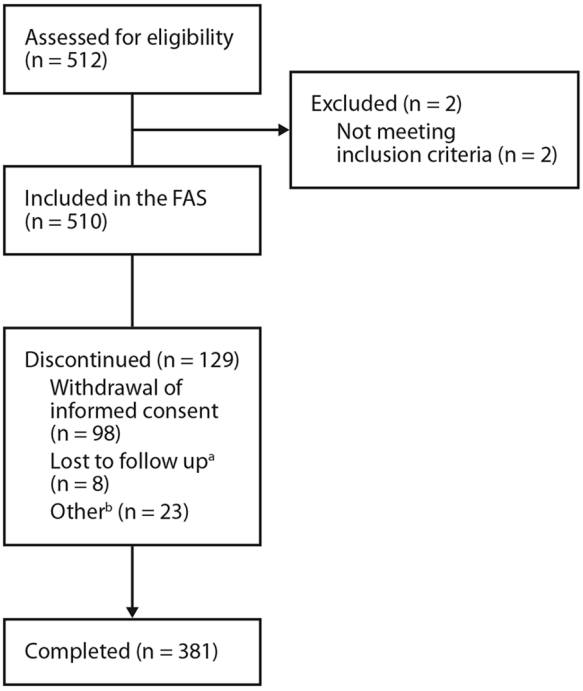

Figure 1. Patient flow.
[a]Not willing to attend hospital visit or unable to be contacted.
[b]Parent/caregiver terminated treatment due to perceived improvement in patient's condition.
FAS, full analysis set.

control status (e.g. patients'/caregivers' attitude towards asthma medication, asthma control status, level of education, comorbidity, severity and duration of asthma, and age) were analysed using univariate and multivariate regression analyses (a stepwise algorithm for variable inclusion was performed; variables with a p value ≤ 0.15 were subsequently included in a multivariate analysis).

Sample size

Previous studies have reported a median treatment adherence of 87% with an interquartile range of 70–94% for preschool children;[12] based on an assumption of normal distribution and a drop-out rate of 20%, a sample size of approximately 500 patients will provide a 95% confidence level with the width of $\pm 1.8\%$.

Results

Patients

Of 512 enrolled patients, 510 were included in the FAS. Overall, 381 patients completed the study (Figure 1). Patient characteristics are given in Table 1.

Of the 510 patients included in the FAS, 504 (98.8%) were prescribed budesonide as long-term home nebulizer ICS therapy. The prescribed dose of budesonide was 1.20 ± 0.57 mg/day (or a 1:1 budesonide-equivalent dose of beclomethasone if this ICS was prescribed).[13] Prescribed ICS therapy may have differed at each visit for any given patient due to the observational nature of the study.

Treatment adherence

The median treatment adherence reported by electronic monitoring devices was 69.9%, lower than the median treatment adherence reported by caregivers (77.9%). Regardless of the method of reporting treatment adherence, there was a slight decrease in median adherence over the course of the study: electronically monitored treatment adherence dropped from 78.1% at visit 2 to 72.5% at visit 3 and 67.8% at visit 4 [Figure 2(a)].

Nonadherence, defined as not following the asthma medication prescription for more than 1 day in the period between visits, was reported by 39.6%, 35.5% and 40.2% of patients at visits 2, 3 and 4, respectively. The most common reason for nonadherence was forgetting medication instructions (Supplemental Table 1).

According to the electronic monitoring devices, most patients had an overall adherence level of $\geq 50\%$ to $<80\%$, whereas caregivers judged most patients' adherence level to be $\geq 80\%$ to $\leq 120\%$ (Supplemental Table 2).

Asthma control

GINA-2016-defined asthma control improved over the course of the study. The proportion of patients with well-controlled asthma increased from 12.0% at baseline (visit 1) to 51.4%, 67.0% and 77.5% at visits 2, 3 and 4, respectively [Figure 2(b)].

In each level of adherence (defined as $<50\%$, $\geq 50\%$ to $<80\%$, $\geq 80\%$ to $\leq 120\%$, $>120\%$) at each visit, a large proportion of patients had well-controlled asthma (Supplemental Tables 3 and 4). The relationship between asthma control and electronically reported adherence or caregiver-reported adherence was similar (Supplemental Tables 3 and 4).

Table 1. Patient characteristics.

	***n*=510**
Age (years), mean (±SD)	3.53 (±2.42)
Age, *n* (%)	
<0 years to ⩽5 years	397 (78.0)
<5 years to ⩽12 years	108 (21.2)
>12 years	4 (0.8)
Sex, *n* (%)	
Male	343 (67.4)
Female	166 (32.6)
Asthma severity, *n* (%)	
Mild	300 (59.1)
Moderate	173 (34.1)
Severe	35 (6.9)
Family history of asthma, *n* (%)	
Yes	65 (12.8)
No	444 (87.2)
Living environment, *n* (%)	
Rural	144 (28.3)
Urban	365 (71.7)
Home nebulizer therapy within 1 year before enrolment, *n* (%)	
Yes	235 (46.3)
No	273 (53.7)
Allergy history, *n* (%)	
Yes	197 (38.9)
No	309 (61.1)
Number of emergency visits/hospitalizations due to asthma in the previous year, *n* (%)	
⩾1	216 (42.4)
<1	293 (57.6)
Prescribed regimen, *n* (%)	
Budesonide	504 (98.8)
Beclomethasone	2 (0.4)
Budesonide and beclomethasone	4 (0.8)
Prescribed dose for budesonide, mg/day (±SD)	1.20 (±0.57)

SD, standard deviation.

Asthma severity

At baseline (visit 1), 300 (59.1%), 173 (34.1%) and 35 (6.9%) patients had mild, moderate, and severe asthma, respectively. At 12 weeks (visit 4), the proportion of patients with mild asthma had increased to 96.0%, and the proportion of patients with moderate and severe asthma had decreased to 3.8% and 0.3%, respectively [Figure 2(c)].

Factors associated with treatment adherence

Caregivers' attitudes to treatment, age, comorbidity, household income, and length of time between asthma diagnosis and study enrolment reached significance ($p < 0.15$) in a stepwise variable selection procedure and were included in a multivariate analysis (see Supplemental Table 5 for all variables included in the univariate analysis).

A multivariate linear regression analysis showed that increased time between asthma diagnosis and study enrolment was a significant predictor of increased adherence to asthma medication [coefficient: 0.01, $p = 0.0138$; 95% confidence interval (CI): 0.00, 0.01; Table 2].

Factors associated with asthma control

While treatment adherence was a significant predictor of control status in the univariate analysis (Supplemental Table 6), it did not reach significance in the multivariate logistic regression analysis (Table 3).

Length of time between asthma diagnosis and study enrolment was a predictive factor for good asthma control [odds ratio (OR) = 1.00, $p = 0.0466$; 95% CI: 1.00, 1.00]. The attitude of caregivers towards asthma: medication was also a predictor for asthma control (Table 3):

- (1) strongly agreeing with 'In the near future, it may become difficult for me to let my child take their asthma medication' was a significant predictor for poor asthma control (OR = 0.09, $p = 0.0425$; 95% CI: <0.01, 0.92);
- (2) disagreeing with 'Medication does not help or is not necessary for long-term use' was a significant predictor for good asthma control (OR = 3.16, $p = 0.0197$; 95% CI: 1.20, 8.29).

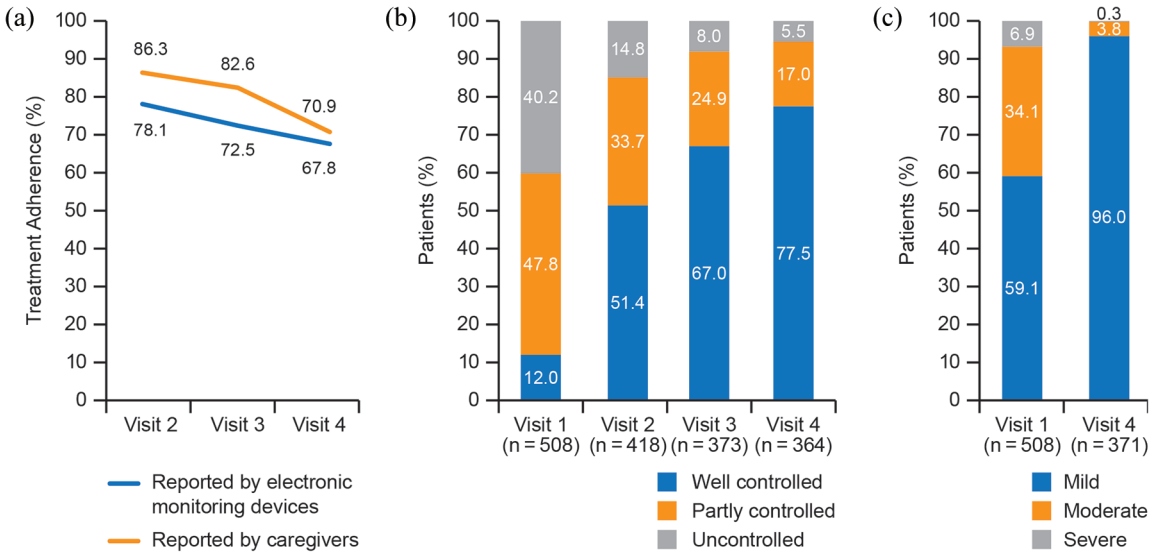

Figure 2. Changes in treatment adherence, asthma control and asthma severity over the course of the study. (a) Treatment adherence reported by electronic monitoring devices or by caregivers; (b) asthma control status across visits 1–4; and (c) asthma severity at visits 1 and 4.

Sensitivity analyses

The PPS consisted of 491 patients, excluding 13 enrolled patients whose post-baseline data were missing and 8 with major protocol deviations (i.e. violating inclusion criteria or lacking prescription frequency data). Median treatment adherence reported by electronic monitoring devices and by caregivers in the PPS [69.9% (interquartile range (IQR): 50.5, 84.8) *versus* 77.8% (IQR: 52.1, 91.1)] was equivalent to those in the FAS. The proportion of patients with well-controlled asthma changed from 11.6% at visit 1 to 51.3%, 67.2% and 77.4% at visits 2–4, respectively, similar to the percentages in the FAS (Supplemental Table 7). Also, no evident differences in the proportions of patients with different levels of asthma severity at visits 1 and 4 were found between the PPS and FAS (Supplemental Table 7).

Discussion

To the best of our knowledge, this study is the first multicentre real-world study in China to record adherence to home nebulization of ICS treatment in asthmatic children using electronic monitoring devices.

In the present study, the median treatment adherence rate reported by portable home nebulizer devices was 69.9%, which compares favourably with many previous reports among children in other regions worldwide: the median electronically monitored adherence was 58.4% and 46%, respectively, in two studies in the USA,[6,14,15] changing from 54% and 41% at month 4 to 47% and 31.5% at month 12 in patients with controlled and uncontrolled asthma, respectively, in a study from Brazil,[16] and 49.5% in a study from The Netherlands.[17] Results of the present study also compared favourably with other studies in China investigating treatment adherence in patients with asthma (adults or children).[18–20] Furthermore, the World Health Organization reported that mean adherence was approximately 50% based on key studies in adults and children.[21] Most of these studies reported adherence to metered-dose inhaler (MDI);[6,14–17] comparatively, our results suggest that a home nebulizer device may facilitate better treatment adherence in paediatric patients.

Self- or caregiver-reported adherence is another common method of recording adherence to asthma treatment. This method comes at a lower cost than monitoring adherence electronically; however, this method is subjective and can therefore lead to reporting inaccuracies (caregiver reports were previously found to be only 60% accurate).[7] Measuring treatment adherence using electronic monitoring devices is considered the gold standard method for accurate reporting of adherence because every use is recorded digitally.[7]

Table 2. Analysis of factors associated with treatment adherence (electronic monitoring) using multivariate linear regression model.

Variable	Category	Coefficient (95% CI)	*p* value
Length of time between asthma diagnosis and study enrolment		0.01 (0.00, 0.01)	0.0138
Insurance status	Urban residents' basic medical insurance	5.41 (−3.15, 13.98)	0.2150
	New rural co-operative medical system	6.09 (−2.87, 15.06)	0.1824
	Commercial medical insurance	4.09 (−9.62, 17.81)	0.5577
	Other medical insurance	−12.91 (−32.25, 6.43)	0.1902
	No medical insurance	0	
Caregivers' attitudes on asthma medication			
I sometimes worry about diminishing effectiveness of the medication over time	Strongly agree	7.75 (−19.22, 34.72)	0.5727
	Agree	8.45 (−18.21, 35.11)	0.5338
	Neutral	1.97 (−25.22, 29.17)	0.8866
	Disagree	5.52 (−22.44, 33.49)	0.6982
	Strongly disagree	0	
	No medical insurance	0	
Caregivers' knowledge of asthma			
Can asthma be life threatening?	Yes	2.04 (−4.26, 8.35)	0.5242
	No	0	
Do you think children with asthma need long-term medication?	Yes, in accordance with a doctor's suggestions	−1.79 (−8.59, 5.00)	0.6040
	No, there is no need for medication when a child is asymptomatic	−8.86 (−18.08, 0.36)	0.0596
	Do not know	0	

CI, confidence interval.

We used this gold standard method alongside caregiver reports in our study and found that the rate of electronically monitored treatment adherence was lower than that reported by caregivers (77.9%). These findings support the notion that treatment adherence is often overestimated by parents/caregivers. The discrepancy between caregiver-reported adherence and actual adherence has been noted previously.[6]

Uni- and multivariate analyses showed that an increased time between diagnosis and study enrolment (i.e. a longer course of disease) was a significant predictor for increased adherence. In the study by Ma *et al.*, only 22.9% of newly diagnosed patients reported good treatment adherence, compared with 63.9% with a history of asthma demonstrating good adherence.[18] These observations may be due to patients or caregivers benefiting from having time to gain experience of the disease and its management, and this could underlie the increased rate of adherence observed in our study compared with previous reports.[6,14–17]

Despite a good median treatment adherence across all patients, over the course of this 12-week

Table 3. Analysis of factors associated with asthma control status using multivariate logistic regression model.

Variable	Category	OR (95% CI)	*p* value
Treatment adherence	Yes	0.64 (0.37, 1.13)	0.1241
	No	1	
Length of time between asthma diagnosis and study enrolment		1.00 (1.00, 1.00)	0.0466
Number of emergency room visits due to asthma in the past 12 months		1.24 (0.98, 1.58)	0.0702
Number of hospitalizations due to asthma in the past 12 months		1.19 (0.83, 1.70)	0.3430
Father's education level	Elementary school	0.81 (0.09, 7.33)	0.8521
	High school	0.53 (0.10, 2.83)	0.4577
	University degree	0.94 (0.21, 4.18)	0.9312
	Master's degree or above	1	
Mother's education level	Unschooled	0.07 (<0.01, 6.42)	0.2515
	Elementary school	0.44 (0.05, 3.87)	0.4603
	High school	1.19 (0.22, 6.61)	0.8391
	University degree	0.81 (0.19, 3.54)	0.7819
	Master's degree or above	1	
Caregivers' attitudes to asthma medication			
With long-term use, medication will prevent my child's asthma from becoming worse	Strongly agree	3.34 (0.50, 22.37)	0.2139
	Agree	3.18 (0.53, 19.15)	0.2070
	Neutral	2.34 (0.37, 14.69)	0.3650
	Disagree	1.75 (0.28, 11.16)	0.5513
	Strongly disagree	1	
Medication does not help or is not necessary for long-term use	Strongly agree	3.21 (0.54, 19.23)	0.2015
	Agree	1.86 (0.66, 5.19)	0.2383
	Neutral	1.67 (0.64, 4.31)	0.2919
	Disagree	3.16 (1.20, 8.29)	0.0197
	Strongly disagree	1	
In the near future, it may become difficult for me to let my child take their asthma medication	Strongly agree	0.09 (<0.01, 0.92)	0.0425
	Agree	0.18 (0.02, 1.68)	0.1313
	Neutral	0.23 (0.02, 2.19)	0.2006
	Disagree	0.11 (0.01, 1.01)	0.0512
	Strongly disagree	1	

(Continued)

Table 3. (Continued)

Variable	Category	OR (95% CI)	*p* value
Caregivers' knowledge of asthma			
What is asthma?	Infectious disease	0.97 (0.37, 2.54)	0.9523
	Chronic inflammatory disease	1.41 (0.61, 3.25)	0.4173
	Contagious disease	>9999.99 (<0.01, >9999.99)	0.9897
	Do not know	1	

CI, confidence interval; OR, odds ratio.

study, treatment adherence decreased regardless of the method of reporting. This phenomenon has been observed previously in paediatric patients with asthma,[5,6,16,18,22] and may be due to patients and caregivers falling into certain behaviours that lead to a decline in treatment adherence over time. Contributors to a lack of adherence include forgetting medication instructions, insufficient caregiver education on the importance of adherence, short-term symptom relief, and concerns about side effects,[18,23] which may be improved by approaches such as using electronic monitoring devices incorporating reminder alarms[24,25] and patient and caregiver education.[18,26,27]

The proportion of patients with well-controlled and mild asthma increased, while that with uncontrolled and severe asthma decreased over the course of the study. We reported a more rapid increase in the proportion of patients with GINA-defined controlled asthma compared with patients treated with beclomethasone dipropionate and chlorofluorocarbon *via* pressurised MDI (pMDI) plus albuterol pMDI for as-needed symptom relief (0%, 17.6%, 41.2% and 62.7% at baseline and month 4, 8 and 12, respectively).[16] Furthermore, a retrospective analysis of adult and paediatric patients with asthma ($n=8188$) prescribed ICS/LABA delivered by dry-powder inhaler or pMDI reported that at the end of the study (6 or 12 months) only 18% had GINA-defined controlled asthma.[28] Together, these studies suggest that home nebulization of ICS therapy may facilitate a more rapid improvement in asthma control compared with other methods. The type of nebulizer used may also impact adherence and efficacy; our findings complement those of Zhou *et al*, who demonstrated that using a 'smart' nebulizer incorporating electronic monitoring to administer ICS therapy resulted in higher adherence rates and significantly improved clinical outcomes compared with conventional nebulizer use.[19]

Uni- and multivariate analyses showed that increased time between diagnosis and study enrolment was a significant predictor of good asthma control. We also found that a negative caregiver attitude was associated with poorer asthma control, perhaps due to a reduced treatment adherence or less care being taken when using the nebulizer. An association between treatment adherence and asthma control has been reported before.[15] However, another study showed that intermittent therapy with high-dose (1 mg twice daily) budesonide provided similar benefits to paediatric asthma patients in terms of exacerbation reduction compared with low-dose daily therapy (0.5 mg nightly).[29] In the present study, an association between treatment adherence and asthma control was not found.

Given that the treatment adherence decreased over time, we recommend that asthma management efforts be centred around patient and caregiver education that focuses on strategies to increase adherence. A focus on the importance of adherence to ICS treatment may prove vital for patients and caregivers with less experience or less knowledge of asthma and its treatment. These concepts are supported by O'Byrne *et al.*, who suggest that poor asthma control is driven in part by insufficient use of ICS, and that the reason for

this is inconsistent and suboptimal education and advice given to the patient and/or caregiver by their physician.[30]

One limitation of this study is that patients at tertiary hospitals may not be representative of the whole population of China, and the adherence of these patients may not represent the adherence of patients treated in secondary or community hospitals. In addition, the use of onsite visits and diary entries to record adherence may inadvertently lead to an increase in adherence when compared with a strategy comprising only passive methods of recording nebulizer use and less frequent onsite visits. Since patients/caregivers were aware that their adherence was going to be recorded, this may have influenced their compliance with prescriptions, leading to better adherence and patient outcomes. Moreover, the high adherence and good control of asthma observed in this study might be related to the use of nebulizers, which are simple and not prone to user errors compared with other inhalers (MDI or dry-powder inhaler), and therefore the results may not be generalizable to patients using other inhaler devices.

Conclusion

Results of this study show that the rate of adherence to home nebulizer treatment in Chinese paediatric patients is good relative to prior reports in other countries and compared with other methods of ICS delivery. Furthermore, GINA-defined asthma control improved as the duration of treatment increased. We conclude that home nebulization of ICS is an effective long-term treatment method for paediatric patients with asthma.

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Authors' contributions

DZ, DC, LL, YZ, YS, CZ, LZ, JP, QC, TA and QN contributed equally to the design of the study, drafted the initial manuscript, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethics approval and consent to participate

The study has been approved by ethic committees of participating study centres. Signed and dated consent was obtained from patients, patients' parents, or guardians for all participants. The study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice and Good Publication Practice guidelines, and the applicable legislation on non-interventional studies and observational studies.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available *via* the AstraZeneca Group of Companies – Data Request Portal at: https://astrazenecagroup-dt.pharmacm.com/DT/Home.

More information on AstraZeneca's clinical trials disclosure policy is available at: http://astrazenecagrouptrials.pharmacm.com//ST/Submission/Disclosure.

Supplemental material

The reviews of this paper are available via the supplemental material section.

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References

1. Guo X, Li Z, Ling W, *et al.* Epidemiology of childhood asthma in mainland China (1988–2014): a meta-analysis. *Allergy Asthma Proc* 2018; 39: 15–29.
2. Hong J, Bao Y, Chen A, *et al.* Chinese guidelines for childhood asthma 2016: major updates,

recommendations and key regional data. *J Asthma* 2018; 55: 1138–1146.

3. Global Initiative for Asthma. Global strategy for asthma management and prevention (updated 2020), https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf (2020, accessed 23 October 2020).
4. Coutts JA, Gibson NA and Paton JY. Measuring compliance with inhaled medication in asthma. *Arch Dis Child* 1992; 67: 332–333.
5. Jentzsch NS, Camargos PA, Colosimo EA, *et al.* Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods. *Allergy* 2009; 64: 1458–1462.
6. Milgrom H, Bender B, Ackerson L, *et al.* Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol* 1996; 98: 1051–1057.
7. Boulet LP, Vervloet D, Magar Y, *et al.* Adherence: the goal to control asthma. *Clin Chest Med* 2012; 33: 405–417.
8. Pearce CJ and Fleming L. Adherence to medication in children and adolescents with asthma: methods for monitoring and intervention. *Expert Rev Clin Immunol* 2018; 14: 1055–1063.
9. Global Initiative for Asthma. Global strategy for asthma management and prevention, https://ginasthma.org/wp-content/uploads/2016/04/GINA-2016-main-report_tracked.pdf (2016, accessed 23 October 2020).
10. Subspecialty Group of Respiratory Diseases SoP, Chinese Medical Association. [Guideline for the diagnosis and optimal management of asthma in children (2016)]. *Zhonghua Er Ke Za Zhi* 2016; 54: 167–181.
11. Li M, Zhang Q, Shi W-J, *et al.* Epidemiological survey and analysis of asthma in children aged 0-14 years old in urban and rural areas of Chengdu region. *Transl Pediatr* 2013; 2: 160–166.
12. Klok T, Kaptein AA, Duiverman EJ, *et al.* Long-term adherence to inhaled corticosteroids in children with asthma: observational study. *Respir Med* 2015; 109: 1114–1119.
13. Abdullah AK and Khan S. Evidence-based selection of inhaled corticosteroid for treatment of chronic asthma. *J Asthma* 2007; 44: 1–12.
14. Walders N, Kopel SJ, Koinis-Mitchell D, *et al.* Patterns of quick-relief and long-term controller medication use in pediatric asthma. *J Pediatr* 2005; 146: 177–182.
15. Klok T, Kaptein AA, Duiverman EJ, *et al.* It's the adherence, stupid (that determines asthma control in preschool children)! *Eur Respir J* 2014; 43: 783–791.
16. Jentzsch NS, Camargos P, Sarinho ES, *et al.* Adherence rate to beclomethasone dipropionate and the level of asthma control. *Respir Med* 2012; 106: 338–343.
17. Vasbinder E, Dahhan N, Wolf B, *et al.* The association of ethnicity with electronically measured adherence to inhaled corticosteroids in children. *Eur J Clin Pharmacol* 2013; 69: 683–690.
18. Ma Q, Luo G, Zhou X, *et al.* Self-reported reasons for treatment non-adherence in Chinese asthma patients: a 24-week prospective telephone follow-up study. *Clin Respir J* 2018; 12: 262–268.
19. Zhou Y, Lu Y, Zhu H, *et al.* Short-term effect of a smart nebulizing device on adherence to inhaled corticosteroid therapy in asthma predictive index-positive wheezing children. *Patient Prefer Adherence* 2018; 12: 861–868.
20. Zhong N, Lin J, Zheng J, *et al.* Uncontrolled asthma and its risk factors in adult Chinese asthma patients. *Ther Adv Respir Dis* 2016; 10: 507–517.
21. Bender B, Boulet LP, Chaustre I, *et al.* Asthma. In: Sabaté E (ed.) *Adherence to long-term therapies: evidence for action*. Geneva, Switzerland: World Health Organization; 2003. pp. 47–58.
22. Jan RL, Wang JY, Huang MC, *et al.* An internet-based interactive telemonitoring system for improving childhood asthma outcomes in Taiwan. *Telemed J E Health* 2007; 13: 257–268.
23. Xu J, Yin Y, Zhang H, *et al.* Paediatric asthma control under a community management model in China: a protocol for a prospective multicentre cohort study. *BMJ Open* 2017; 7: e015741.
24. Anderson WC III and Szefler SJ. New and future strategies to improve asthma control in children. *J Allergy Clin Immunol* 2015; 136: 848–859.
25. Morton RW, Elphick HE, Rigby AS, *et al.* STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. *Thorax* 2017; 72: 347–354.
26. Butz AM, Huss K, Mudd K, *et al.* Asthma management practices at home in young inner-city children. *J Asthma* 2004; 41: 433–444.
27. Zhao J, Shen K, Xiang L, *et al.* The knowledge, attitudes and practices of parents of children with asthma in 29 cities of China: a multi-center study. *BMC Pediatr* 2013; 13: 20.

28. O'Byrne PM, Reddel HK, Eriksson G, *et al.* Measuring asthma control: a comparison of three classification systems. *Eur Respir J* 2010; 36: 269–276.

29. Zeiger RS, Mauger D, Bacharier LB, *et al.* Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011; 365: 1990–2001.

30. O'Byrne PM, Jenkins C and Bateman ED. The paradoxes of asthma management: time for a new approach? *Eur Respir J* 2017; 50: 1701103.