ORIGINAL ARTICLE
ASTHMA

Nonadherence in the era of severe asthma biologics and thermoplasty

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Preventer adherence is underrecognised and must be confirmed objectively prior to initiating novel asthma treatment http://ow.ly/Kc1X30iysYD

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ABSTRACT Nonadherence to inhaled preventers impairs asthma control. Electronic monitoring devices (EMDs) can objectively measure adherence. Their use has not been reported in difficult asthma patients potentially suitable for novel therapies, *i.e.* biologics and bronchial thermoplasty.

Consecutive patients with difficult asthma were assessed for eligibility for novel therapies. Medication adherence, defined as taking >75% of prescribed doses, was assessed by EMD and compared with standardised clinician assessment over an 8-week period.

Among 69 difficult asthma patients, adherence could not be analysed in 13, due to device incompatibility or malfunction. Nonadherence was confirmed in 20 out of 45 (44.4%) patients. Clinical assessment of nonadherence was insensitive (physician 15%, nurse 28%). Serum eosinophils were higher in nonadherent patients. Including 11 patients with possible nonadherence (device refused or not returned) increased the nonadherence rate to 31 out of 56 (55%) patients. Severe asthma criteria were fulfilled by 59 out of 69 patients. 47 were eligible for novel therapies, with confirmed nonadherence in 16 out of 32 (50%) patients with EMD data; including seven patients with possible nonadherence increased the nonadherence rate to 23 out of 39 (59%).

At least half the patients eligible for novel therapies were nonadherent to preventers. Nonadherence was often undetectable by clinical assessments. Preventer adherence must be confirmed objectively before employing novel severe asthma therapies.

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Introduction

"Difficult asthma" is a term referring to patients who remain uncontrolled despite treatment at Steps 4 and 5 of the Global Initiative for Asthma (GINA) guidelines [1]. The overall prevalence of difficult asthma has been estimated at between 10% and 17% of asthma patients [1, 2].

A major contributor to difficult asthma is unsuppressed airway inflammation consequent to relative corticosteroid insensitivity [3]. In such patients, novel treatment options are now licensed for specific disease phenotypes, specifically monoclonal biologics targeting IgE (omalizumab) and the interleukin (IL)-5 pathways (mepolizumab, reslizumab) or bronchial thermoplasty [4–7]. Such treatments are expensive and should only be considered after standard therapy (including high-dose inhaled corticosteroids (ICSs), usually in combination with a long-acting bronchodilator) has been optimised [8–11].

Medication adherence can be defined as "the degree to which the medication use of the patient corresponds to the prescribed regimen" [12, 13]. Patient nonadherence to medications can thus vary over time, and can be both intentional (*e.g.* due to fear of side-effects) and nonintentional (*e.g.* due to cost or forgetfulness). Identifying and addressing nonadherence to inhaled respiratory medications has been identified as an urgent priority for international policy makers [14]. Medication nonadherence is particularly prevalent in difficult asthma, with previous estimates of nonadherence of ∼50% by prescription refills [15–17]. Assessing prescription refills can be challenging if there are multiple prescribers and dispensing pharmacies. In clinical practice, preventer adherence is usually assessed subjectively by the treating health professional or based on patient self-report, which are both notoriously inaccurate [18]. However, inaccurate subjective assessments can have significant consequences: a large proportion of patients with difficult asthma also have severe biological asthma and poorer clinical outcomes are seen in those who are nonadherent to inhaled preventers [19]. Additionally, if nonadherence remains undetected in difficult asthma, patients may proceed inappropriately to targeted biological therapy or thermoplasty [9].

Detailed objective measurements of adherence may now be obtained by electronic monitoring devices (EMDs) [20–22]. These devices can be placed on the patient's preventer inhaler on initial contact and data downloaded at the next clinic visit. EMDs have been used to examine nonadherence in asthma, but data regarding their utility in difficult asthma are limited.

We hypothesised that nonadherence in difficult asthma remains a significant issue in the era of novel severe asthma therapies. We used an EMD to objectively measure preventer nonadherence in difficult asthma and compared this with structured, albeit subjective, clinician assessment. We specifically examined the rate of nonadherence among patients suitable for anti-IgE and anti-IL-5 biologics or thermoplasty.

Materials and methods

Patients were referred with difficult asthma if their treating respiratory or allergy specialists had difficulty with their asthma management. Reasons for referral (usually multiple) were diagnostic dilemma, poor symptom control, frequent or severe exacerbations, poor lung function, or patient factors, including comorbidities and suspected nonadherence [23].

Patients undergo systematic evaluation over 6 months in three visits to: confirm the diagnosis of severe asthma, to identify and address exacerbating triggers or comorbidities (including anxiety and depression, vocal cord dysfunction, dysfunctional breathing, gastro-oesophageal reflux disease, obstructive sleep apnoea, allergic rhinitis, and chronic rhinosinusitis), and to determine the inflammatory phenotype to facilitate selection of optimal medical therapy, including targeted biologics [24]. As previously described, the assessment process is supported by questionnaires for the assessment of the patient's asthma control (Asthma Control Test (ACT)) [25] and quality of life (Asthma Quality of Life Questionnaire (AQLQ)) [26], as well as a comorbidity questionnaire battery, an electronic platform and a panel discussion for each patient [27–29]. Permission was obtained for all administered questionnaires.

Our centre prescribes asthma biologics [30], but does not perform bronchial thermoplasty.

This study included consecutive patients who entered the difficult asthma protocol between May 1, 2015 and December 31, 2016. The study was approved by the Alfred Health Ethics Committee (285/15).

Eligibility for novel asthma therapies

For this study, patients were categorised as eligible for biologics if they met American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for severe and uncontrolled asthma [24], and had either an eosinophilic (blood eosinophil count $\geqslant 0.3\times10^{9}$ L^{-1}; suitable for anti-IL-5 therapy) or allergic phenotype (serum IgE level $\geqslant 30$ kU·mL^{-1} and sensitisation to an aeroallergen based on skin testing or serum-specific IgE; suitable for anti-IgE therapy).

Patients were categorised as eligible for thermoplasty based on entry criteria for the Research in Severe Asthma (RISA) trial [7]; high-dose ICS/LABA inhalers, pre-bronchodilator forced expiratory volume in 1 s >50% predicted, positive bronchoprovocation or bronchodilator response, uncontrolled asthma and no current smoking nor prior smoking history of ⩾10 pack-years.

Adherence assessment

At the first clinic visit, the difficult asthma protocol physician would explain to each patient that the routine procedure for all patients was to provide an EMD for objective monitoring of asthma management if their inhaler device was compatible. Language was aimed to be neutral and nonjudgemental. A Smartinhaler device (Adherium, Auckland, New Zealand) was attached to the patient's preventer inhaler. EMDs were available for a variety of ICS or ICS/long-acting β-agonist (LABA) combination inhalers, specifically metered dose inhalers and dry powder devices for Flixotide (fluticasone propionate), Seretide (salmeterol and fluticasone propionate), Pulmicort (budesonide) and Symbicort (budesonide and formoterol). EMDs were not available for other ICS or ICS/LABA combination inhalers. The EMD was able to record the timing of the doses taken according to the number prescribed for morning or evening.

Data were downloaded at the scheduled follow-up visit at the 2-month time-point. Data collected included the date, time and number of actuations, preventing "dose dumping".

For the purposes of this study, the patient was considered adherent if >75% of prescribed doses were actuated at the times they were prescribed, based on an increased risk of exacerbations reported below this cut-point [31]. Day-to-day adherence rate was not reported. Patients were defined as possibly nonadherent if they declined to have the device added to their inhaler or did not return the device despite reminders.

Adherence was also assessed at the first visit by the referring specialist, the patient, the difficult asthma clinic respiratory physician and a clinical asthma nurse. Referring specialists also completed a standardised referral form and could indicate whether they felt the patient was nonadherent.

At the first clinic visit during systematic evaluation, self-reported adherence was documented if the patient agreed with the following statement "I follow my medication plan".

The difficult asthma clinic specialist assessed patient adherence using the components of the validated Adult Asthma Adherence Questionnaire [32], including specific questions surrounding forgetfulness, a perception that preventer treatment was unnecessary, fear of side-effects and cost. Following the assessment, physicians were prompted to estimate inhaler adherence as <50%, 50–75% or >75%.

At the first clinic visit, all patients underwent clinical asthma nurse assessment and education to address the patient's understanding of asthma, inhaler technique and adherence. The asthma nurse fitted the electronic device to the patient's inhaler. Following assessment, nursing staff were prompted to estimate adherence as "good", "partial" or "poor". Patients estimated to have "partial" or "poor" adherence were considered nonadherent.

Statistical analysis

Data analysis was performed using SPSS version 22 (IBM, Armonk, NY, USA). Categorical variables are presented as percentages (frequency) and continuous variables are presented as mean or median values with standard deviation and/or range. T-test for comparison of means and Fisher's exact or Chi-squared tests for comparison of proportions were performed where appropriate.

Results

During the study period, 71 consecutive patients underwent systematic evaluation. Two patients did not have asthma, had their inhalers discontinued and were excluded from further analysis. Baseline characteristics of the remaining 69 patients are presented in table 1.

In this difficult asthma cohort, poor asthma control and quality of life were reflected in the average ACT and AQLQ scores. 86% of patients were on GINA Step 4 or 5 asthma treatment. 59 out of 69 (85%) patients had severe asthma, all of whom had uncontrolled asthma (as defined by the ERS/ATS guidelines) [24].

Eligibility for biologics and thermoplasty

30 (43.5%) patients were eligible for anti-IgE therapy and 22 (31.9%) for anti-IL-5 therapy, with 38 (55%) potential candidates for either. 26 patients (37.7%) were eligible for thermoplasty. In total, 47 (68%) patients were eligible for a biologic or thermoplasty, or both (figure 1).

EMD adherence assessment

69 patients were considered for an EMD. The flow of patients through each stage of the study is shown in figure 2.

Adherence outcomes for all 69 difficult asthma patients are shown in figure 3a. "Unknown adherence": adherence status could not be objectively assessed in 13 patients; 10 did not use a preventer with a compatible EMD and three returned a device which malfunctioned. "Possible nonadherence": another 11 exhibited behaviour suggestive of nonadherence; two patients refused the EMD and nine did not return the device, some of whom reported the device as lost. "Confirmed nonadherence": of 45 patients who returned a device with usable data, 20 (44.4%) were nonadherent; mean±SD rate of nonadherence was 51.4±20.8% (interquartile range (IQR) 38–65%). "Confirmed adherence": 25 out of 45 (55.6%) patients had documented preventer adherence of >75%; mean±SD rate of adherence was 89±6.3% (IQR 84–95%).

If patients with confirmed and possible (those who refused or did not return the EMD) nonadherence were grouped together, the overall nonadherence rate increased to 31 out of 56 (55.3%) patients.

Confirmed nonadherent patients had higher mean serum eosinophils (0.42×10^9 *versus* 0.22×10^9 L^{-1}; $p<0.05$) than confirmed adherent patients. There were no other significant associations of other clinical features that differed between adherent and nonadherent patients (table 2). The mean ICS dose (µg fluticasone equivalent) was not significantly different in patients who were adherent (982 µg) or nonadherent (850 µg).

TABLE 1 Baseline characteristics

Subjects	69
Age years	52±14.2 (19–76)
Female	41 (59.4)
Smoking status	
Never-smoker	46 (66.7)
Ex-smoker	22 (31.9)
Current smoker	1 (1.4)
BMI kg·m^{-2}	30±6.9
Early-onset asthma <18 years	34 (49.3)
Pre-bronchodilator FEV_1 % pred	62±20.2
Change in FEV_1 % pred following bronchodilator	14.2±15
FEV_1/FVC %	61±15.4
Airflow obstruction at baseline (FEV_1 <80%, FEV_1/FVC <70%)	41 (59.4)
Variable airflow obstruction demonstrable	61 (88.4)
⩾12% and ⩾200 mL improvement in FEV_1 following bronchodilator	47 (77)
>12% variability in peak flow charting over 2 weeks	12 (19.7)
Positive bronchial provocation challenge test with mannitol	2 (3.3)
Blood eosinophils ×10^9 L^{-1}	0.33±0.33 (0–1.73)
Eosinophils ⩾0.3×10^9 L^{-1}	28 (40.6)
***F*ENO ppb**	36±31.2 (4–137)
IgE kU·L^{-1}	524±1006 (2–4880)
Atopic[#]	47 (68.1)
ACT score[¶]	13.6±5.19
AQLQ score[+]	4.19±1.4
Exacerbations in last 12 months requiring oral (>3 days or increase in 20 mg from baseline prednisolone dose) or intravenous corticosteroids	5±4.7 (0–30)
Frequency of asthma exacerbations in 12 months	
0	4 (5.8)
1	8 (11.6)
2	2 (15.9)
⩾3	46 (66.7)
On ICS/LABA combination	66 (95.7)
Total ICS dose µg fluticasone equivalent	992±538 (0–3200)
On OCSs	17 (24.6)
Total OCS dose mg	8.7±6.23 (1–25)
Severe asthma by ATS/ERS guidelines	59 (85.5)
Anxiety and depression[§]	24 (35)

Data are presented as n, mean±SD (range), mean±SD or n (%). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; *F*ENO: exhaled nitric oxide fraction; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; OCS: oral corticosteroid; ATS: American Thoracic Society; ERS: European Respiratory Society. [#]: positive skin prick test or serum-specific IgE to commonly tested aeroallergens; [¶]: <15 indicating poor control; [+]: out of 7, high score indicating better quality of life; [§]: diagnosis based on presence of clinical symptoms and Hospital Anxiety and Depression Scale [33] score ⩾11 or known history on treatment.

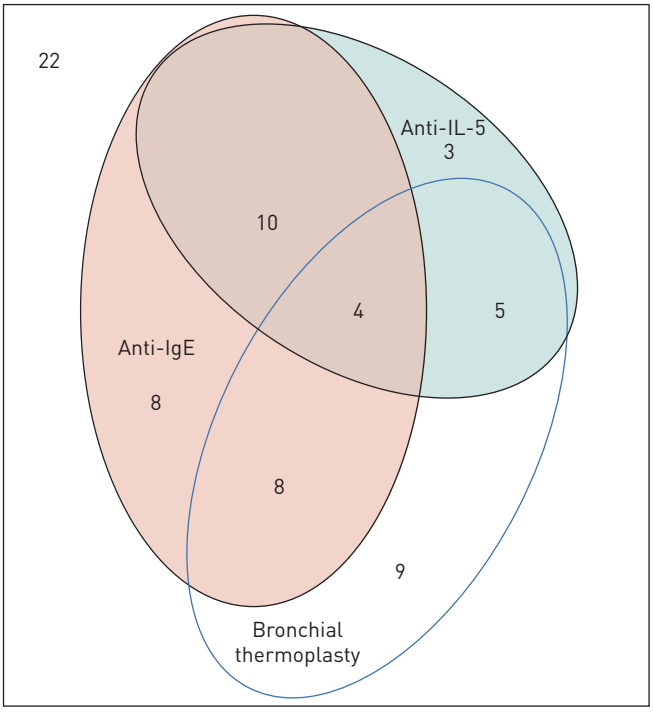

FIGURE 1 Patients eligible for novel asthma therapies: biologics and bronchial thermoplasty (47 out of 69). IL: interleukin.

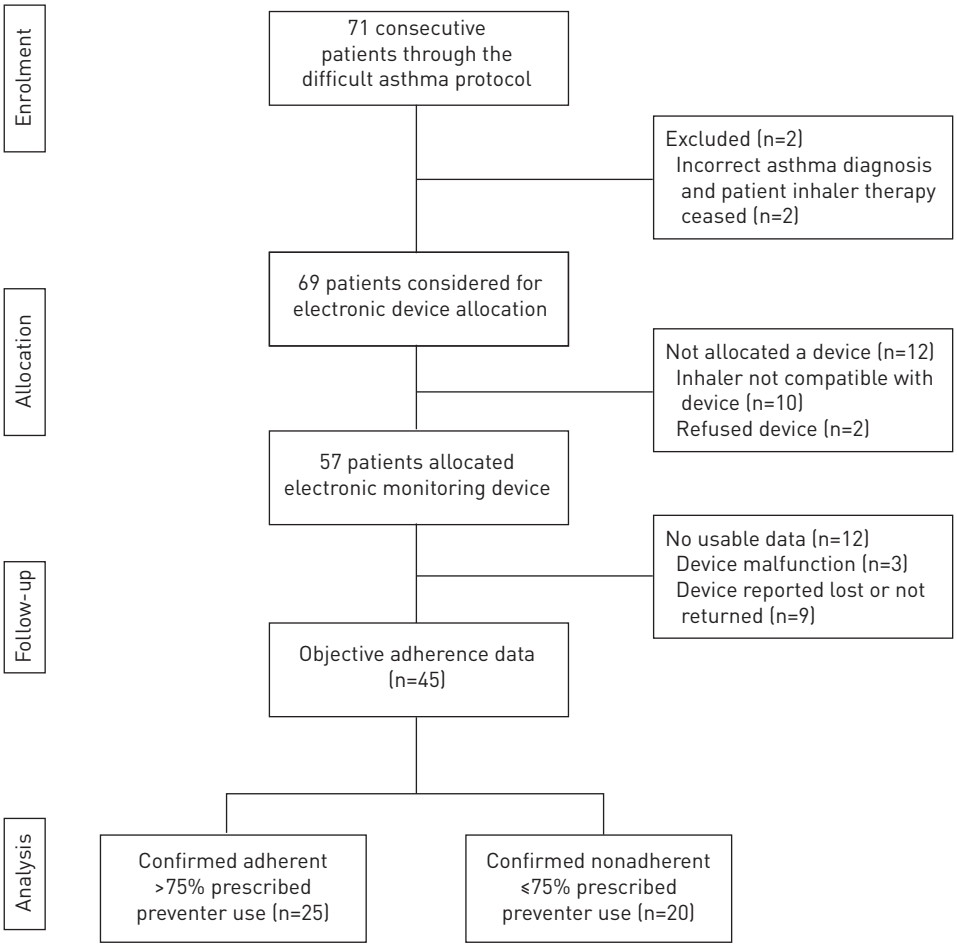

FIGURE 2 Patient flow through each stage of the study.

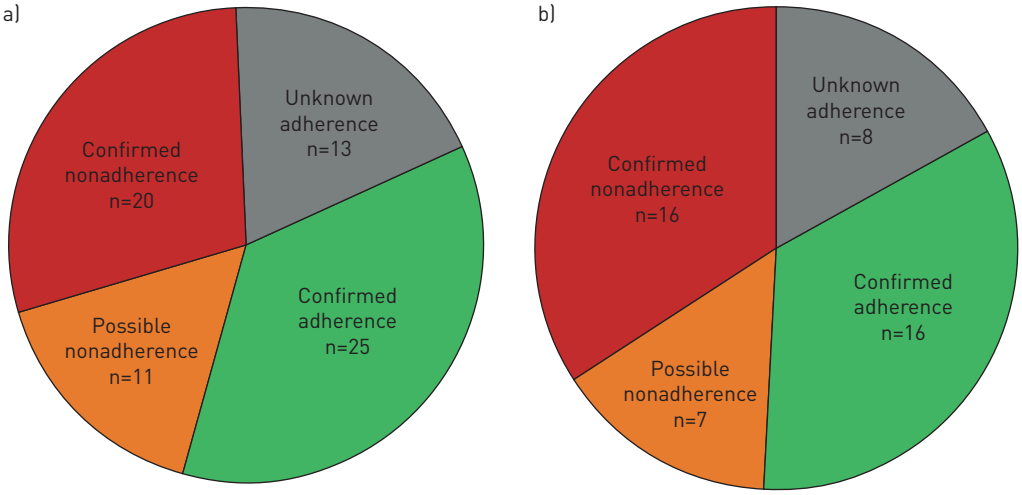

FIGURE 3 Patients with unknown adherence, confirmed adherence, possible nonadherence and confirmed nonadherence in a) all 69 difficult asthma patients and b) the 47 patients eligible for novel asthma therapies (biologics or thermoplasty).

Among 47 patients either eligible for biologics or bronchial thermoplasty, adherence could not be assessed in eight (EMD-incompatible inhaler or device malfunction) and nonadherence was possible in seven (refused or did not return the EMD). 32 patients returned usable EMD data, of whom 16 out of 32 (50%) had confirmed nonadherence on EMD assessment. Combining confirmed and possible nonadherent populations gave a nonadherence rate among those eligible for novel therapies of 23 out of 39 (59%) patients (figure 3b).

TABLE 2 Characteristics of adherent compared with nonadherent patients

	Adherent	Nonadherent	p-value
Subjects	25	20	
Age years	54±12	54±16	NS
Female	13 (52)	11 (55)	NS
Smoking status			
Never-smoker	14 (56)	14 (70)	
Ex-smoker	11 (44)	5 (25)	
Current smoker	0 (0)	1 (5)	
BMI kg·m^{-2}	30±5	31±8	NS
Early-onset asthma <18 years	13 (52)	8 (40)	NS
Pre-bronchodilator FEV_1 % pred	65±22	60±18	NS
FEV_1/FVC %	61±17	58±12	NS
Airflow obstruction at baseline (FEV_1 <80%, FEV_1/FVC <70%)	14 (56)	13 (65)	NS
Blood eosinophils ×10^9 L^{-1}	0.22±0.21	0.42±0.34	<0.05
F_{ENO} ppb	27.22±18	41.4±30	NS
IgE kU·L^{-1}	369.5±736	551.5±1030	NS
ACT score[#]	12.2±4	13.5±6	NS
AQLQ score[¶]	4.34±1	3.99±1	NS
Exacerbations in last 12 months requiring oral (>3 days or increase in 20 mg from baseline prednisolone dose) or intravenous corticosteroids	3.5±18	2.8±2	NS
Total ICS dose µg fluticasone equivalent	982±444	850±379	NS
Total OCS dose mg	4±2	9.4±5	NS
Severe asthma by ATS/ERS guidelines	21 (84)	19 (95)	NS
Anxiety or depression[+]	11 (44)	7 (35)	NS

Data are presented as n, mean±SD or n (%). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: exhaled nitric oxide fraction; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; ICS: inhaled corticosteroid; OCS: oral corticosteroid; ATS: American Thoracic Society; ERS: European Respiratory Society; NS: nonsignificant. [#]: <15 indicating poor control; [¶]: out of 7, high score indicating better quality of life; [+]: diagnosis based on presence of clinical symptoms and Hospital Anxiety and Depression Scale [33] score ⩾11 or known history on treatment.

Subjective adherence assessment

Two of the 45 patients with EMD data had nonadherence identified by the referring specialist as a reason for the patient's poor asthma control. Two patients admitted that they did not follow their prescribed medication plan. Protocol physicians identified five patients as being nonadherent (of these, two were proven to be adherent objectively), whereas asthma nurses identified seven patients as being nonadherent (of these, two were also proven to be adherent objectively) (figure 4).

Compared with the EMD, the sensitivity and specificity of physician detection of nonadherence was 15% (95% CI 3.2–37.9%) and 92% (95% CI 74–99%), respectively. The sensitivity and specificity of asthma nurse assessment was 27.8% (95% CI 9.7–53.5%) and 91.67% (95% CI 73–99%), respectively (figure 4).

Discussion

Among patients otherwise suitable for novel severe asthma therapies, our study shows an alarmingly high rate of nonadherence. Furthermore, most cases of nonadherence remained undetected despite a series of subjective clinical assessments by the referring respiratory or allergy specialist, the difficult asthma protocol specialist and asthma nursing staff. This finding emphasises the indispensable value of assessing nonadherence objectively prior to initiating biologics or performing thermoplasty for severe asthma [9].

Previous studies have shown high rates of nonadherence among difficult asthma patients by monitoring prescription refills, which gives an indication of long-term medication use [16, 34, 35]. This can be difficult to perform in health systems such as our Australian setting, where patients may obtain preventers through multiple prescribers and at multiple dispensing pharmacies of their choice. Prescription refills and other indirect methods of measuring medication adherence such as canister weights also cannot confirm that a patient actually takes their medication at the correct time. We therefore chose to use EMDs, which provide detailed information on inhaler use.

The true prevalence of nonadherence in our difficult asthma population likely lies between 44% and 55%, consistent with previous studies [15, 16]. However, the finding of even greater nonadherence among patients suitable for biologics or thermoplasty supports the premise that nonadherence is intrinsically linked to more severe markers of disease. Indeed, we found that nonadherent patients had higher peripheral eosinophil counts. A previous study also found greater sputum eosinophilia among nonadherent patients [16]. Thus, an indication for instituting severe asthma biologics may also indicate a higher risk of nonadherence. Interestingly, severity of asthma symptoms, frequency of exacerbations or poorer lung function did not seem to influence rates of medication adherence. Similarly, prevalence of anxiety and depression was not increased among patients who were found to be nonadherent.

The optimal method to assess preventer adherence remains unclear and EMDs are not infallible. An initial pilot study of the device we used recorded a mean accuracy of 97% [20]. In a clinical trial of 303 patients incorporating extensive pre- and post-study checks, there was a 6.5% malfunction rate. In addition, 3.5% of devices were lost or thrown away by participants [36]. Other trials have reported higher malfunction rates of between 15% and 20% [37, 38].

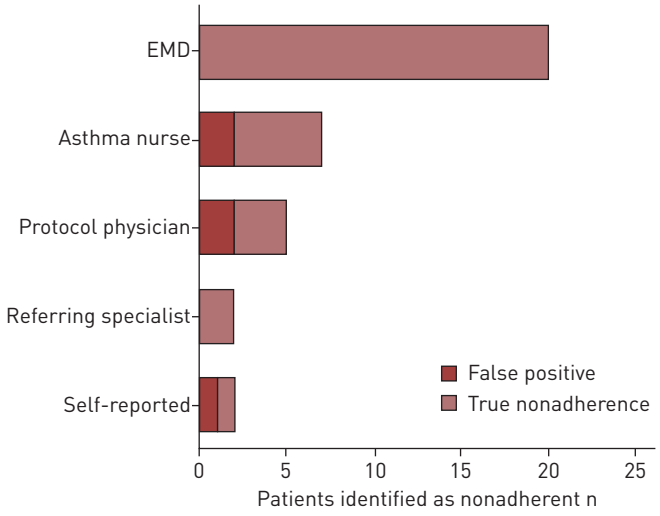

FIGURE 4 Detection of nonadherence by subjective methods in 45 difficult asthma patients with objective data from the electronic monitoring device (EMD).

In our study, adherence could not be assessed objectively in 19% of patients either due to EMD-incompatible inhalers (14.4%) or device malfunction (5.3%). Patients possibly subverted the process in another 11 cases (16%), either by refusing or not returning the device despite repeated requests; such behaviour has been reported in previous pragmatic studies [22] and in our view could also represent possible medication nonadherence. We acknowledge that some patients may have felt uncomfortable with being monitored and this may have influenced the acceptance of the device or failure-to-return rate. We chose not to implement financial incentives to return the device.

Consequently, objective EMD data was obtained in less than two-thirds of our cohort. The failure-to-return rate is higher than in previously reported clinical trials, reflecting the challenges of real-life evaluation of consecutive clinical patients, which is always more difficult than when participants have been selected for a trial. Due to cost, some guidelines have questioned the utility of EMDs in the management of asthma, outside of the research setting [39]. The EMDs cost approximately USD150 (AUD200) in 2018 prices, but this could be considered trivial in comparison with the cost of severe asthma biologics or thermoplasty procedures. However, the true cost of monitoring does go beyond the cost of devices, such as the costs of time required to manage these in the clinic setting: education of the patient, testing to reduce malfunction rates and the efforts required to ensure their return.

Self-reporting of nonadherence was unreliable and poorly sensitive in our cohort, consistent with previous studies [40, 41]. Subjective clinical assessments were also poorly sensitive for detecting EMD-confirmed nonadherence. This was despite assessment by an expert and experienced difficult asthma service, multiple assessments by three health professionals (referring physician, treating physician and asthma nurse), and the use of standardised assessments including a validated adherence tool [32]. In light of this, objective assessments are clearly indispensable to adequately detect nonadherence. Interestingly, a minority of patients who were deemed poorly adherent by clinical assessment were subsequently proven to be adherent by electronic monitoring. Although described as "false positives", this cohort may have improved their adherence behaviour in the knowledge that they were being monitored. Nevertheless, these patients may have had their access to advanced therapies inappropriately limited by the healthcare team if reliance had been placed solely on subjective measurement of adherence.

25% of our patient cohort was on oral steroids. It could be argued that patients with uncontrolled asthma despite oral steroids may require a novel therapy such as a biologic irrespective of their adherence to inhaled steroids. However, we would argue that patients nonadherent to inhaled therapy would also be likely to be nonadherent to oral medication [15]. (Assessing adherence to oral corticosteroids was beyond the scope of this study due to nonavailability of in-house serum prednisolone levels.) In addition, it is a government funding body requirement in Australia that adherence to inhaled steroids is documented prior to prescription of biologics.

The aim of our study was to detect nonadherence, not to manage it, and this study was not designed to report on longitudinal outcomes. However, an EMD can be used to provide feedback and deliver an audio reminder to the patient. These measures have been shown to improve adherence [21] and, in a paediatric population, led to fewer exacerbations requiring oral corticosteroids or hospitalisation [22]. Such benefits have yet to be shown in a difficult asthma population and would be an interesting area for future research. The overall outcomes of our 6-month, three-visit systematic assessment protocol have been previously reported [29].

This study was conducted at a single centre with an interest in difficult asthma, so the generalisability of our findings is unknown. However, the rate of nonadherence in our cohort is consistent with those reported from other difficult asthma centres in other health systems [15, 16]. Nonadherence in nonsevere asthma is even more prevalent. In a cross-sectional community study of patients with asthma (over half of which were "well controlled"), 65% of respondents were nonadherent to a preventer <4 days a week [42]. For this study, we defined eligibility for severe asthma biologics based on generic criteria and suitability for thermoplasty based on inclusion criteria for the single randomised RISA trial of thermoplasty in severe asthma [7]. However, additional criteria may apply according to local licensing authorities and funding arrangements. We further acknowledge that nonadherent patients identified by EMD may be a heterogeneous group that we were unable to stratify further in this study. Patients taking <75% of prescribed doses could be described as partially adherent and probably represent a diverse group of patients. However, this cut-off was chosen because published data demonstrates such patients are at an increased risk of adverse asthma outcomes [31]. While EMDs can confirm that an inhaler is actuated, they cannot determine if the patient actually inhaled the medication nor whether inhaler technique was satisfactory. Nevertheless, we maintain that EMD-confirmed nonadherence is a robust finding. The provision of the EMD alerted patients that their adherence was being monitored. It is possible that the degree of nonadherence might have been even greater had patients been unaware of monitoring, *i.e.* the Hawthorne effect [43].

We conclude that preventer nonadherence in difficult asthma remains disturbingly high in the era of novel (and expensive) therapies for severe asthma. There are a multitude of factors that may underlie nonadherence and we advocate for further research to be carried out in this area. Subjective assessment of adherence is highly unreliable, so objective assessments are imperative prior to initiating severe asthma biologics or performing thermoplasty.

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References

1 Reddel HK, Bateman ED, Becker A, *et al.* A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; 46: 622–639.
2 Hekking P-PW, Wener RR, Amelink M, *et al.* The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015; 135: 896–902.
3 Hew M, Chung KF. Corticosteroid insensitivity in severe asthma: significance, mechanisms and aetiology. *Intern Med J* 2010; 40: 323–334.
4 Bousquet J, Siergiejko Z, Świebocka E, *et al.* Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. *Allergy* 2011; 66: 671–678.
5 Ortega HG, Liu MC, Pavord ID, *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198–1207.
6 Castro M, Zangrilli J, Wechsler ME, *et al.* Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3: 355–366.
7 Pavord ID, Cox G, Thomson NC, *et al.* Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med* 2007; 176: 1185–1191.
8 Draikiwicz S, Oppenheimer J. Use of biological agents in asthma. *Chest* 2017; 151: 249–251.
9 Barnes PJ. Counterpoint: will new anti-eosinophilic drugs be useful in asthma management? No. *Chest* 2017; 151: 17–20.
10 Whittington MD, McQueen RB, Ollendorf DA, *et al.* Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Ann Allergy Asthma Immunol* 2016; 118: 220–225.
11 Zafari Z, Sadatsafavi M, Marra CA, *et al.* Cost-effectiveness of bronchial thermoplasty, omalizumab, and standard therapy for moderate-to-severe allergic asthma. *PLoS One* 2016; 11: e0146003.
12 Vrijens B, Dima AL, Van Ganse E, *et al.* What we mean when we talk about adherence in respiratory medicine. *J Allergy Clin Immunol Pract* 2016; 4: 802–812.
13 World Health Organization. Adherence to long-term therapies: evidence for action. 2003. www.who.int/chp/knowledge/publications/adherence_full_report.pdf Date last accessed: February 23, 2018.
14 van Boven JFM, Lavorini F, Dekhuijzen PNR, *et al.* Urging Europe to put non-adherence to inhaled respiratory medication higher on the policy agenda: a report from the First European Congress on Adherence to Therapy. *Eur Respir J* 2017; 49: 1700076.
15 Gamble J, Stevenson M, McClean E, *et al.* The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009; 180: 817–822.
16 Murphy AC, Proeschal A, Brightling CE, *et al.* The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax* 2012; 67: 751–753.
17 Boulet L-P, Vervloet D, Magar Y, *et al.* Adherence. *Clin Chest Med* 2012; 33: 405–417.
18 Patel M, Perrin K, Pritchard A, *et al.* Accuracy of patient self-report as a measure of inhaled asthma medication use. *Respirology* 2013; 18: 546–552.
19 Williams LK, Pladevall M, Xi H, *et al.* Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004; 114: 1288–1293.
20 Foster JM, Smith L, Usherwood T, *et al.* The reliability and patient acceptability of the SmartTrack device: a new electronic monitor and reminder device for metered dose inhalers. *J Asthma* 2012; 49: 657–662.
21 Chan AHY, Stewart AW, Harrison J, *et al.* The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *Lancet Respir Med* 2015; 3: 210–219.
22 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* 2016; 72: 347–354.
23 Radhakrishna N, Tay TR, Hore-Lacy F, *et al.* Profile of difficult to treat asthma patients referred for systematic assessment. *Respir Med* 2016; 117: 166–173.
24 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.
25 Nathan RA, Sorkness CA, Kosinski M, *et al.* Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; 113: 59–65.
26 Juniper EF, Guyatt GH, Epstein RS, *et al.* Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992; 47: 76–83.

27 Radhakrishna N, Tay TR, Hore-Lacy F, *et al.* Validated questionnaires heighten detection of difficult asthma comorbidities. *J Asthma* 2017; 54: 294–299.
28 Tay TR, Radhakrishna N, Hore-Lacy F, *et al.* Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life. *Respirology* 2016; 21: 1384–1390.
29 Tay TR, Lee J, Radhakrishna N, *et al.* A structured approach to specialist-referred difficult asthma patients improves control of comorbidities and enhances asthma outcomes. *J Allergy Clin Immunol Pract* 2017; 5: 956–964.
30 Gibson PG, Reddel H, McDonald VM, *et al.* Effectiveness and response predictors of omalizumab in a severe allergic asthma population with a high prevalence of comorbidities: the Australian Xolair Registry. *Intern Med J* 2016; 46: 1054–1062.
31 Williams LK, Peterson EL, Wells K, *et al.* Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol* 2011; 128: 1185–1191.
32 Schatz M, Zeiger RS, Yang S-J, *et al.* Development and preliminary validation of the Adult Asthma Adherence Questionnaire™. *J Allergy Clin Immunol Pract* 2013; 1: 280–288.
33 Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67: 361–370.
34 Robinson DS, Campbell DA, Durham SR, *et al.* Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003; 22: 478–483.
35 Heaney LG, Horne R. Non-adherence in difficult asthma: time to take it seriously. *Thorax* 2011; 67: 268–270.
36 Patel M, Pilcher J, Travers J, *et al.* Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. *J Allergy Clin Immunol Pract* 2013; 1: 83–91.
37 Apter AJ, Wang X, Bogen DK, *et al.* Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128: 516–523.
38 Rand C, Bilderback A, Schiller K, *et al.* Adherence with montelukast or fluticasone in a long-term clinical trial: results from the Mild Asthma Montelukast Versus Inhaled Corticosteroid Trial. *J Allergy Clin Immunol* 2007; 119: 916–923.
39 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. 2014. www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014 Date last accessed: February 23, 2018.
40 Krishnan JA, Bender BG, Wamboldt FS, *et al.* Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. *J Allergy Clin Immunol* 2012; 129: 112–118.
41 Foster JM, Smith L, Bosnic-Anticevich SZ, *et al.* Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. *Intern Med J* 2012; 42: e136–e144.
42 Reddel HK, Sawyer SM, Everett PW, *et al.* Asthma control in Australia: a cross-sectional web-based survey in a nationally representative population. *Med J Aust* 2015; 202: 492–496.
43 Braunholtz DA, Edwards SJL, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epidemiol* 2001; 54: 217–224.