ORIGINAL ARTICLE

Assessing Adherence by Combining the Test of Adherence to Inhalers With Pharmacy Refill Records

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J Investig Allergol Clin Immunol 2021; Vol. 31(1): 58-64
doi: 10.18176/jiaci.0461

Abstract

Background: The Global Initiative for Asthma (GINA) recommends the concurrent use of self-report and pharmacy refill data to assess treatment adherence. However, clinical evidence to support this combined approach is limited.
Objective: To determine nonadherence to inhaler medication based on a validated questionnaire (Test of Adherence to Inhalers; TAI) and prescription refill data in a community sample of patients with chronic obstructive pulmonary disease (COPD) or asthma. Secondarily, we sought to determine the degree of concordance between these two measures.
Methods: Cross-sectional, observational multicenter study in patients with asthma or COPD. Sociodemographic and clinical data were obtained from clinical records. Refill data were retrieved from electronic pharmacy databases. Participants completed the 12-item TAI during a single visit as part of routine care. Nonadherence was defined as TAI <50 or <80% pharmacy refill rate (PRR) in the previous 6 months.
Results: A total of 816 patients (mean age, 60) were included. Nonadherence rates were 58.1% (TAI) and 28.6% (PRR) compared with 64.6% for the combined data ($P<.0001$). Concordance between the 2 measures was weak ($\kappa=0.205$).
Conclusions: These findings confirm the GINA recommendations, indicating that concomitant use of the TAI and pharmacy refill data identifies a higher percentage of nonadherent asthma or COPD patients than either instrument alone.

Key words: Asthma. Adherence to therapy. COPD. Self-reported success. Patient compliance. Nebulizer.

Resumen

Antecedentes: La *Global Initiative for Asthma* (GINA) recomienda el uso combinado de cuestionarios autocumplimentados y el registro de la retirada de la medicación mediante la receta electrónica (RERFF) para determinar el nivel de adhesión terapéutica. Sin embargo, la evidencia para apoyar esta recomendación es limitada.
Objetivos: El objetivo del presente estudio fue determinar el nivel de adhesión a los inhaladores utilizando la información proporcionada mediante el Test de Adhesión a los Inhaladores (TAI-12), junto al RERFF, en un grupo de pacientes con asma o con Enfermedad Pulmonar Obstructiva Crónica (EPOC). Un objetivo secundario fue determinar el grado de concordancia entre ambos métodos.
Métodos: Estudio observacional, transversal y multicéntrico en pacientes diagnosticados con asma o EPOC. Se recogieron las características demográficas y clínicas de los registros clínicos. Los datos de retirada de inhaladores se recogieron en el RERFF. Los participantes cumplimentaron el TAI-12 durante una sola visita en el contexto de la atención clínica rutinaria. Se definió "baja adherencia" como TAI <50 o RERFF <80% en los 6 meses previos.
Resultados: Se incluyeron 816 pacientes (edad media, 60 años). Las tasas de baja adherencia fueron 58,1% (TAI) y 28,6% (RERFF) versus 64,6% para la combinación de los dos instrumentos (TAI+RERFF; p<0,0001). La concordancia entre las dos medidas fue débil (kappa de Cohen = 0,205).
Conclusiones: Estos resultados confirman las recomendaciones de GINA, indicando que el uso de la combinación del TAI y la RERFF incrementa la capacidad para identificar la baja adherencia terapéutica, comparada con la del TAI o RERFF por separado.

Palabras clave: Asma. Adhesión terapéutica. EPOC. Éxito auto-comunicado. Cumplimiento del paciente. Nebulizador.

Introduction

Up to 60% of patients do not fully adhere to their prescribed treatment regimen [1-3]. Suboptimal adherence leads to worse clinical outcomes, more exacerbations, and higher morbidity and mortality rates [4-8]. A wide range of factors can negatively impact adherence to prescription medications [9,10], including demographic variables, disease-related factors, adverse effects, comorbidities, and lifestyle factors. Inhaler-specific factors that can influence adherence include improper inhaling technique, difficulties associated with the use of multiple devices, complex treatment regimens, and prolonged treatment duration [10-12].

Numerous methods, both objective and subjective, are available to assess treatment adherence in patients with asthma and chronic obstructive pulmonary disease (COPD) [13]. Although the most reliable methods are objective measures such as electronic monitoring devices and blood tests, the use of these instruments in routine clinical practice is impractical. By contrast, validated self-report questionnaires, such as the Test of Adherence to Inhalers (TAI) [12,14,15], offer clinicians a straightforward, inexpensive approach to assessing adherence, with acceptable reliability. In many regions, objective refill data can be obtained electronically from pharmacy dispensing records. Due to the simplicity, low cost, and acceptable reliability of both methods, the Global Initiative for Asthma (GINA) and other recent guidelines recommend using them concurrently to assess treatment adherence [16,17]. However, clinical evidence to support this combined approach to assessing adherence to inhalers is limited [18].

In this context, the aim of the present cross-sectional study was to determine nonadherence to inhaler medication based on a validated questionnaire (TAI) and prescription refill data in a community sample of patients with COPD or asthma. We also sought to determine the degree of concordance between these 2 measures.

Methods

Study Design and Patients

This was a cross-sectional, multicenter study. The inclusion criteria were as follows: (*1*) age ≥18 years; (*2*) diagnosis of asthma or COPD; (*3*) treatment with inhalers for at least the previous 6 months; and (*4*) signed informed consent. The only exclusion criterion was inability to use an inhaler due to physical limitations. Asthma was defined according to the Global Initiative for Asthma (GINA) criteria [16] and COPD according to the Global Initiative for Chronic Obstructive Lung Disease [19].

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Hospital de la Santa Creu i Sant Pau Barcelona (Spain) (CHI-ASM-2015-02 [RETAI]). The study was registered with the Spanish Agency of Medicines and Medical Devices. Written informed consent was obtained from all participants. All personal data were anonymized.

Study Procedures

Investigators from 26 centers in Spain were selected to participate in the study. Patients were recruited from the following departments/sites: pulmonology (11 centers; 42.3%), allergology (n=5; 19.2%), internal medicine (n=5; 19.2%), and primary care centers (n=5; 19.2%). Each center was expected to enroll 30 consecutive patients (15 patients with COPD and 15 with asthma) during the 7-month inclusion period (September 2016 to April 2017). All study data were obtained from the clinical interview conducted during a single visit as a part of routine care or from the patient's medical record. At this visit, the physician obtained the patient's informed consent and recorded all relevant demographic and clinical data. All participating patients completed the TAI. In addition, patients with COPD or asthma completed, respectively, the COPD Assessment Test [20] or the Asthma Control Test [21]. All patients underwent spirometry testing, which was performed according to the Spanish Society of Pneumology and Thoracic Surgery guidelines [22] using the reference values for a Mediterranean population [23]. The participating investigators recorded prescription refill data obtained from the electronic pharmacy database.

Evaluation Instruments

The TAI is a 12-item questionnaire with a total score ranging from 10 to 50, which classifies patients as nonadherent when the score is <50. The TAI also identifies the specific type of nonadherent behavior, as follows: erratic (due to forgetfulness), deliberate, or unwitting (due to misunderstanding the dosing schedule and/or poor inhalation technique) [13].

Prescription refill data were obtained from the patients' pharmacy records to determine the number of inhaler devices prescribed by the physician and dispensed by the pharmacy in the previous 6 months. In accordance with standard practice [24], the refill threshold for good adherence was set at ≥80%, which assumes that the patient picked up his/her monthly prescription at least 5 times during the 6-month study period. Thus, any patient with a pharmacy refill rate (PRR) <80% was considered nonadherent. In all cases, adherence was based on the primary inhaler, which was determined by the treating physician. If the prescription involved a combination of drugs in a single inhaler, then this device was considered the primary inhaler. In all other cases, the primary inhaler was the device designed to deliver inhaled corticosteroids (asthma) or long-acting bronchodilators (COPD).

Study Variables

Sociodemographic variables included sex, age, educational level, and occupational status. The baseline clinical variables were diagnosis, years since onset, pre- and post-bronchodilation FVC and FEV_1 values, and smoking status (years smoking and pack-years). The variables related to inhaler use were administration of medication (self-administration/requires help), inhaler training received (yes/no), professional evaluation of inhaling technique (yes/no), number of devices used. Pharmacy refill data included number of devices prescribed and dispensed in the previous 6 months.

Statistical Analysis

A descriptive analysis of the sociodemographic and baseline clinical characteristics of the study population was performed. Data are described as mean (SD) or No. (%), as appropriate. Adherence results in the asthma and COPD subgroups were compared using the *t* test or χ^2 tests. The McNemar test was used to compare adherence rates derived from the TAI and pharmacy data to assess relative bias. Concordance was assessed by determining the κ statistic. The statistical analysis was performed using IBM Statistics for Windows (IBM Corp). Statistical significance was set at $P<.05$.

Results

Baseline Sociodemographic and Clinical Characteristics

A total of 824 patients were recruited, and 816 met all the inclusion criteria. Mean age was 60 years (range, 18-94) and 445 (54.5%) were men. On average, the patients used 1.8 different inhaler devices, with most patients (n=689) using only 1 (266; 32.6%) or 2 (423; 51.8%); the remaining 127 patients used ≥3 (15.6%). Table 1 shows the demographic and clinical characteristics of the study sample.

Adherence

Overall (Table 2, Figure), 28.6% of patients were nonadherent according to the pharmacy data compared with 58.1% according to the TAI (TAI <50 points). According to the PRR, 37.9% of asthma patients were nonadherent compared with 19.3% of patients with COPD ($P<.001$). When both instruments were used in combination, the percentage of nonadherers increased to 64.6%, indicating that the combined data identified more nonadherent patients than either instrument alone. Adherence (mean TAI score) was lower in the asthma group than in the COPD group (45.1 vs 47.0; $P<.001$), with 51.5% of patients with COPD presenting good adherence (TAI, 50) versus 32.3% in the asthma group ($P<.001$).

Concordance Between the TAI and PRR

Table 3 shows the cross-classification of the patients in terms of adherence or nonadherence as assessed by each method (TAI and PRR). Overall, 35.4% of patients were considered adherent (PRR ≥80% and TAI, 50) on both measures while 22.1% were nonadherent. Thus, the 2 tools agreed in 57.5% and disagreed in 42.5% of cases (Table 3). Overall agreement between the 2 measures was weak (κ=0.205) (Table 3).

Most of the patients (Table 1) reported having received previous training in inhaler use (75.5%) and previous verification of their inhalation technique (73.8%). Items 11 and 12 on the TAI are designed to evaluate unwitting nonadherence; as Table 4 shows, patients who previously received training in inhaler use and whose inhaler technique was verified by a professional had significantly higher scores on items 11 and 12.

Table 1. Baseline Patient Sociodemographic and Clinical Characteristics

Variable	All Patients (n=816)[a]	Asthma (n=406)[a]	COPD (n=410)[a]
Age, y	60.1 (17.2)	49.8 (16.7)	70.2 (10.2)
Male sex, No. (%)	445 (54.5)	129 (31.8)	316 (77.1)
Years since diagnosis	12.7 (11.0)	16.0 (13.0)	9.4 (7.3)
FEV_1 (preBD), %	68.1 (24.0)	82.3 (18.7)	51.1 (17.9)
FVC (preBD), %	81.2 (20.6)	90.2 (17.0)	70.5 (19.4)
FEV_1/FVC (preBD)	0.7 (0.3)	0.8 (0.4)	0.5 (0.1)
FEV_1 (postBD), %	72.1 (25.2)	88.5 (18.3)	53.5 (17.9)
FVC (postBD)	83.9 (20.4)	93.3 (16.2)	73.0 (19.3)
FEV_1/FVC (postBD), %	0.7 (0.3)	0.8 (0.3)	0.5 (0.1)
Never smoker, No. (%)	304 (37)	283 (70)	21 (5)
Received training in inhaler use, No. (%)	616 (75.5)	331 (81.5)	285 (69.5)
Proper inhaler technique verified, No. (%)	602 (73.8)	325 (80.0)	277 (67.6)
Number of devices used (range, 1-4)	1.8 (0.7)	1.8 (0.7)	1.9 (0.7)
Charlson comorbidity index	3.27 (2.8)	1.35 (1.67)	5.17 (2.36)
Mean ACT or CAT score	Not applicable	19.3 (4.8)	17.1 (7.6)
Uncontrolled disease (ACT <20 or CAT >10), No. (%)	Not applicable	176 (43.8%)	319 (77.8%)

Abbreviations: ACT, Asthma Control Test; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; preBD, prebronchodilator testing; postBD, postbronchodilator testing.
[a]All data given are expressed as mean (SD) unless otherwise indicated.

Table 2. Adherence According to TAI and Pharmacy Refill Rate

	All (n=816)	Asthma Group (n=406)	COPD Group (n=410)	*P* Value[a]
TAI				
Total score, mean (SD)	46.0 (6.0)	45.1 (6.6)	47.0 (5.2)	<.001
Level of adherence, No. (%)				
Good (50 points)	342 (41.9)	131 (32.3)	211 (51.5)	<.001
Intermediate (46-49 points)	234 (28.7)	134 (33.0)	100 (24.4)	
Poor (≤45 points)	240 (29.4)	141 (34.7)	99 (24.1)	
Type of nonadherence, No. (%)[b]				
Erratic	447(45.6)	262 (51.2)	185 (39.5)	<.001
Deliberate	295 (30.1)	166 (32.4)	129 (27.6)	<.005
Unwitting	238 (24.3)	84 (16.4)	154 (32.9)	<.001
Pharmacy Refill Data				
Mean (SD) no. of devices prescribed in previous 6 mo	5.6 (2.3)	5.0 (1.9)	6.3 (2.3)	<.001
Mean (SD) no. of devices filled at the pharmacy in previous 6 mo	4.6 (2.3)	3.8 (2.2)	5.4 (2.2)	<.001
Patients with pharmacy refill rate ≥80% during the previous 6 mo, No. (%)	583 (71.4)	252 (62.1)	331 (80.7)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; TAI, Test of Adherence to Inhalers.
[a]Between asthma and COPD groups. *t* test or χ^2 test, as appropriate.
[b]Erratic nonadherence: due to forgetfulness, changing schedules, or busy lifestyles.
Unwitting nonadherence: inadvertent nonadherence due to failure to understand the treatment protocol.
Deliberate nonadherence: the intentional discontinuation or failure to use the inhaler.

Table 3. Concordance of Adherence as Measured Using the TAI and Pharmacy Refill Rate

Patient Set	10-Item TAI		Bias[b]	Agreement	
PRR	Adherent, No. (%)[a]	Nonadherent, No. (%)	*P* Value	Observed	κ (95% CI)
All					
Adherent	289 (35.4%)	294 (36.0%)	<.001	57.5%	0.20 (0.15- 0.29)
Nonadherent	53 (6.5%)	180 (22.1%)			
Asthma					
Adherent	104 (25.6%)	148 (36.5%)	<.001	56.9%	0.21 (0.12- 0.29)
Nonadherent	27 (6.7%)	127 (31.3%)			
COPD					
Adherent	185 (45.1%)	146 (35.6%)	<.001	58.0%	0.15 (0.07- 0.22)
Nonadherent	26 (6.3%)	53 (12.9%)			

Abbreviations: COPD, chronic obstructive pulmonary disease; PRR, pharmacy refill rate; TAI, Test of Adherence to Inhalers.
[a]Adherence based on TAI was defined as TAI=50; Adherence based on PRR was defined as PRR ≥80%.
[b]McNemar test to compare adherence as measured by TAI or PRR.

Table 4. Association Between Previous Training and Verification of Inhalation Technique and Scores on TAI Items 11-12 (Unwitting Nonadherence Profile)

Mean score on TAI questions 11-12 according to status (yes [scoring 2 points] vs no [1 point]) for inhaler technique training and verification							
		All	*P*[a]	Asthma	*P*[a]	COPD	*P*[a]
Received inhaler technique training	Yes	3.73 (0.51)	<.001	3.80 (0.45)	.016	3.65 (0.56)	<.001
	No	3.44 (0.70)		3.61 (0.61)		3.33 (0.73)	
Inhaler technique verified	Yes	3.75 (0.50)	<.001	3.83 (0.40)	<.001	3.66 (0.58)	<.001
	No	3.40 (0.69)		3.52 (0.69)		3.32 (0.68)	

Abbreviations: COPD, chronic obstructive pulmonary disease; TAI, Test of Adherence to Inhalers.
[a]*t* test.

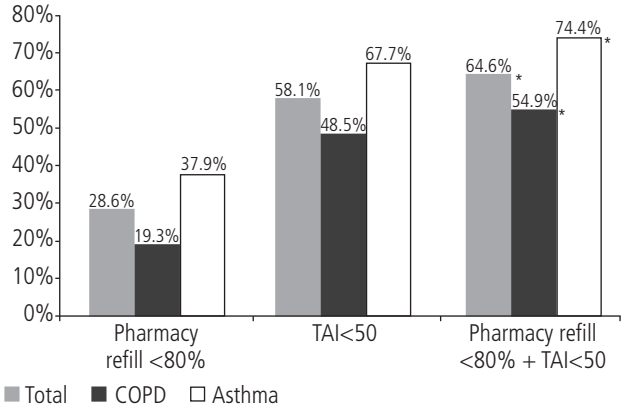

Figure. Percentage of nonadherent patients according to the 10-item Test of Adherence to Inhalers (50 points) and pharmacy refill records. COPD indicates chronic obstructive pulmonary disease; TAI, Test of Adherence to Inhalers.

Discussion

The GINA and other recent guidelines [16,17] recommend the concomitant use of validated self-report questionnaires and pharmacy refill data to identify nonadherent patients. However, this approach has not previously been clinically evaluated. We found, as expected, that the combined use of these 2 methods identified a higher percentage of nonadherent patients (64.6%) than either the TAI (58.1%) or pharmacy refill data (28.6%) separately. These findings support the value of using this multimeasure approach to reliably identify nonadherent patients.

In clinical settings, self-report instruments are the most commonly used measures of adherence due to their low cost, acceptable reliability, and rapid administration time (<10 minutes for the TAI) [25]. An important advantage of the TAI over more general measures of adherence is its capacity to differentiate between the type of nonadherence, namely, erratic, deliberate, or unwitting. This provides the clinician with valuable information that makes it possible to tailor and implement measures and thus improve adherence [14,26]. Another key advantage of the TAI is that it was specifically designed and validated to assess adherence to inhalers.

Pharmacy refill data provide an objective but indirect assessment of adherence—the prescription refill rate. However, the main drawback of this approach to determining adherence is that it can only confirm that the patient has filled the prescription, not whether he/she has taken the medication as prescribed. Despite these disadvantages, pharmacy refill records are noninvasive, widely available, and can be quickly checked by the physician.

Differences in Nonadherence Rates Between the TAI and Pharmacy Refill Data

In terms of each instrument's relative capacity to identify nonadherence, we found that the TAI identified a significantly higher percentage of nonadherent patients than the refill data (58.1% vs 28.6%; Table 2). This important difference in nonadherence rates identified by the 2 measures was unexpected, and the disparity is likely due to multiple factors. First, studies have shown that patients who report nonadherence on self-reports or clinical interview are likely to be telling the truth [13,32]. This would partially explain the discrepancy between the nonadherence rates in our study, as it is conceivable that some patients picked up their prescriptions—thus explaining the "good" adherence identified by the refill data—but then failed to take the medication, subsequently admitting to this failure when completing the TAI. Second, it seems highly probable that the low nonadherence rates detected by the refill data in our study are related to the low cost of inhalers in Spain (which has universal health care coverage). Third, the 26 participating centers in this study were based in different regions of Spain, each of which uses a different electronic database for pharmacy prescriptions: differences between these systems may have affected the results. Finally—and perhaps most importantly—the TAI, which is the only validated self-report instrument that specifically assesses adherence to inhalers, may be more accurate than other widely used measures, such as the Morisky-Green test, which assess adherence to "medications" in general rather than inhalers specifically. In short, the TAI may provide a more accurate measure of nonadherence than other self-report measures, as suggested by the results of the TAI validation study [14], which demonstrated that the psychometric properties of this instrument are significantly better than those of the Morisky-Green test. Moreover, the fact that only 6.5% of patients considered adherent according to the TAI were nonadherent according to pharmacy records further supports the value of the TAI for determining nonadherence.

With regard to concordance, a review conducted by Lehmann et al [3] concluded that prescription refill data and self-report measures are only weakly correlated, a finding that is consistent with our results (κ=0.205). However, de Llano et al [18], who—like us—also used the TAI and pharmacy refill data to assess adherence to inhalers (but only in patients with asthma), reported a moderate correlation between the 2 methods. Moreover, we found that although the 2 methods agreed in 57.5% of cases (35.4% identified as adherent and 22.1% as nonadherent), there was no agreement for the remaining 42.5% of patients. This lack of correlation underscores the value of using 2 different methods to assess adherence [3,16,17]. Indeed, it is precisely this low correlation that supports their combined use, as each method assesses different but complementary aspects of adherence. According to Lehmann et al [3], the combination of direct and indirect methods, as in our study, may increase the reliability and validity of the data collected by overcoming the limitations inherent to each individual method. The authors of a recently published review[27] echoed those recommendations in favor of using multiple measures of adherence, concluding that the use of ≥2measures might allow the strengths of one method to compensate for the weaknesses of the other. Whereas subjective measures (such as self-report questionnaires) can assess patient-related beliefs, barriers to adherence, and the type of nonadherence, objective measures (such as pharmacy refill data) can provide objective data for comparison. The

concomitant use of objective and subjective instruments is likely to provide increased reliability, which explains why this approach is recommended in numerous recent publications, including 2 reviews [3,27], 2 clinical guidelines [16,17], and a recent multidisciplinary consensus Delphi study conducted in Spain [28]. However, given that neither method is 100% accurate, both tools should be applied concomitantly. If either of these tools indicates poor adherence, then the clinician can reasonably assume that the patient is, in fact, nonadherent. This assumption would be further strengthened if both methods indicate nonadherence.

Strengths and Limitations

The present study has several limitations. First, we did not assess adherence using a gold standard such as electronic measuring devices. Thus, the true adherence rate was not determined. However, we did use a validated instrument, the TAI, which has been shown to have good psychometric properties. The TAI is a self-report questionnaire, with all of the limitations inherent to such tools. Similarly, pharmacy refill records also have important limitations, mainly that they only provide indirect evidence about prescription fulfilment but not whether the patient actually took the medication, or if the inhaler was used properly. In addition, we evaluated adherence based on the previous 6 months of refill data, and any refills made in the period immediately prior to or after the study period could have influenced the true adherence rate during the study period. Furthermore, the high adherence rate identified by refill data may be related to the low cost of these medications in Spain; PRRs are likely to be lower in countries in which medication costs are higher. By contrast, the main strengths of this study are the large sample size and the fact that the results confirm the value of concomitantly assessing adherence using 2 methods.

Conclusions

The concomitant use of the Test for Adherence to Inhalers and pharmacy refill records appears to identify a higher proportion of nonadherent patients than either instrument used alone. The first step to improving treatment adherence and clinical outcomes in patients with asthma and COPD is to identify nonadherent patients. However, this requires the use of practical, reliable, and cost-effective measures of adherence such as the TAI and pharmacy refill records. The data presented here support the concomitant use of these 2 measures, thereby confirming the recommendations in the GINA guidelines.

Acknowledgments

We would like thank Bradley Londres for professional English language editing. We also thank the contract research organization, GOC networking, for their contributions.

Funding

The study was supported in part by an unrestricted grant from Chiesi (Spain). The sponsor had no role in the design of this study or in the analyses, data interpretation, and decision to submit results.

Conflicts of Interest

In the last 3 years, VP has received honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, and Novartis. VP has also received financial support to travel to meetings organized by Chiesi and Novartis. VP is a consultant for ALK, AstraZeneca, Boehringer, MundiPharma, and Sanofi. VP has also received funding/grant support for research projects from a variety of governmental agencies and not-for-profit foundations, as well as from AstraZeneca, Chiesi, and Menarini. BGC has received honoraria for speaking at sponsored meetings from AstraZeneca, Teva, Mundipharma, Boehringer-Ingelheim, Chiesi, GSK, and Novartis. BGC has also received financial support to travel to meetings organized by Chiesi, Menarini, and Novartis. BGC acts as a consultant for ALK, AstraZeneca, MundiPharma, Chiesi, and Sanofi and has received funding/grant support for research projects from a variety of governmental agencies and not-for-profit foundations, as well as from Boehringer-Ingelheim, AstraZeneca, Chiesi, and Menarini. JG has received funding to travel to and attend training activities from Menarini, Teva, AstraZeneca, Chiesi, GSK, MundiPharma, and Boehringer. ECS has received funding to travel to and attend training activities from ALK, Menarini, Teva, AstraZeneca, Chiesi, Boehringer, and Novartis. JMV has received honoraria for speaking at sponsored meetings and received financial support to travel from Leti, ALK, AstraZeneca, Chiesi, GSK, TEVA, MundiPharma, and Novartis. IOR has received funding to travel and to attend training activities from GSK, Ferrer, AstraZeneca, and Chiesi.

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Manuscript received June 6, 2019; accepted for publication October 8, 2019.

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