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

Short title: *TAI + Pharmacy Refill Data to assess adherence*

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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 non-adherence 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 multicentre 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. Non-adherence was defined as TAI < 50 or < 80% pharmacy refill rate (PRR) in the last six months.

Results: A total of 816 patients (mean age, 60) were included. Non-adherence rates were 58.1% (TAI) and 28.6% (PRR) versus 64.6% for the combined data (p<.0001). Concordance between the two measures was weak (Cohen's 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 non-adherent asthma or COPD patients than either instrument alone.

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 claves: Adhesión terapéutica, Asma, EPOC, Cumplimiento del paciente

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, side-effects, comorbidities, and life-style factors, among others. 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 these methods, the Global Initiative for Asthma (GINA) and other recent guidelines recommend using both methods 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 this cross-sectional study was to determine non-adherence to inhaler medication based on a validated questionnaire (TAI) and prescription refill data in a community sample of patients with COPD or asthma. Secondarily, we sought to determine the degree of concordance between these two measures.

METHODS

Study design and patients

This was a cross-sectional, multicentre study. Inclusion criteria were as follows: 1) age ≥18 years; 2) diagnosis of asthma or COPD; 3) treatment with inhalers for at least the last 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 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 the 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 centre was expected to enroll 30 consecutive patients (15 patients with COPD and 15 with asthma) during the seven-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 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 predicted values for the 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 non-adherent when scoring < 50. The TAI also identifies the specific type of non-adherent behaviour, 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 last six 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 six-month study period. Thus, any patient with a pharmacy refill rate (PRR) < 80% was considered non-adherent. 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 patient gender, age, educational level, and occupational status. 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). 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 last 6 months.

Statistical analysis

A descriptive analysis of the sociodemographic and baseline clinical characteristics of the study population was performed. Data are described as means (SD) or n (%), as

appropriate. Adherence results in asthma and EPOC subgroups were compared by Student's t-test or chi-square (χ2) tests. McNemar's test was used to compare adherence rates derived from the TAI and pharmacy data to assess relative bias. Concordance was assessed by determining the Cohen's kappa coefficient (κ). Statistical analysis was performed with v.23 of the Statistical Package for the Social Sciences (SPSS-IBM; Chicago, IL, USA). Statistical significance was set at $p<0.05$.

RESULTS

Baseline sociodemographic and clinical characteristics

A total of 824 patients were recruited and 816 met all inclusion criteria. The mean patient 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 either only one (266; 32.6%) or two (423; 51.8%) devices; 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 non-adherent according to the pharmacy data versus 58.1% according to the TAI (TAI < 50 points). According to the PRR, 37.9% of asthma patients were non-adherent vs. 19.3% of patients with COPD ($p<0.001$). When both instruments were used in combination, the percentage of non-adherers increased to 64.6%, indicating that the combined data identified more non-adherent patients than either instrument alone. Adherence (mean TAI score) was lower in the asthma group vs. COPD (45.1 vs. 47.0; $p<0.001$), with 51.5% of patients

with COPD presenting good adherence (TAI=50) versus 32.3% in the asthma groups (p<0.001).

Concordance between the TAI and PRR

Table 3 shows the cross-classification of the patients in terms of adherence or non-adherence 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 non-adherent. Thus, the two tools agreed in 57.5% and disagreed in 42.5% of cases (Table 3). Overall agreement between the two measures was weak (k=0.205) (Table 3).

Most of the patients (Table 1) reported having received previous training in inhaler use (75.5%) and previous verification of inhalation technique (73.8%). Items 11 and 12 on the TAI are designed to evaluate unwitting non-adherence; 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.

DISCUSSION

The GINA and other recent guidelines[16][17] recommend the concomitant use of validated self-report questionnaires and pharmacy refill data to identify non-adherent patients. However, this approach has not been clinically evaluated until now. We found, as expected, that the combined use of these two methods identified a higher percentage of non-adherent patients (64.6%) than either the TAI (58.1%) or pharmacy refill data (28.6%) administered separately. These findings support the value of using this multimeasure approach to reliably identify non-adherent 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 non-adherence—erratic, deliberate, or unwitting, which provides the clinician with valuable information to tailor and implement measures to 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 non-invasive, widely-available, and can be quickly checked by the physician.

Differences in non-adherence rates between the TAI and pharmacy refill data

In terms of each instrument's relative capacity to identify non-adherence, we found that the TAI identified a significantly higher percentage of non-adherent patients than the refill data (58.1% vs. 28.6%; Table 2).   This important difference in non-adherence rates identified by the two measures was unexpected. This large disparity is likely due to multiple different factors.. First, studies have shown that patients who report non-adherence on self-reports or clinical interview are likely to be telling the truth[13,32]. This would partially explain the discrepancy between the non-adherence rates in our

study, as it is conceivable that some patients picked up their prescriptions—which would explain 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 non-adherence 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, and difference among 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 non-adherence 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 non-adherent according to pharmacy records further supports the value of the TAI for determining non-adherence.

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 (kappa=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 two methods. Moreover, we found that although the two methods agreed in 57.5% of cases (35.4% identified as adherent and 22.1% as non-adherent), there was no agreement in the remaining 42.5% of patients. This lack of correlation underscores the value of using two 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 and colleagues, the combination of direct and indirect methods, as in our study, may increase the reliability and validity of the collected data by overcoming the limitations inherent to each individual method[3]. The authors of a recently-published review[27] echoed those recommendations in favor of using multiple measures of adherence, concluding that the use of ≥ two measures might allow the strengths of one method to compensate for the weaknesses of any individual method. Whereas subjective measures (such as self-report questionnaires) can assess patient-related beliefs, barriers to adherence, and the type of non-adherence, 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 two reviews[3,27], two clinical guidelines[16][17], and in 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, non-adherent. This assumption would be further strengthened if both methods indicate non-adherence.

Study 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. Nevertheless, 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 fulfillment but not whether the patient actually took the medication, nor if the inhaler was used properly. In addition, we evaluated adherence based on the last 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. In addition, the high adherence rate identified by refill data may be related to the low cost of these medications in our country; pharmacy refill rates are likely to be lower in countries in which the cost of medication costs is 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 with two methods.

CONCLUSIONS

The concomitant use of the Test for Adherence to Inhalers and pharmacy refill records appears to identify a higher proportion of non-adherent 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 non-adherent 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 two measures, thereby confirming the recommendations in GINA guidelines.

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Author contributions

VP takes responsibility for the integrity of the work as a whole and had full access to all data, including adverse effects. VP drafted the manuscript with critical revision from all co-authors. VP, BGC, JG, ECS, JMV, IOR all contributed substantially to the study design, data analysis and interpretation, and manuscript preparation.

Declaration conflict of interest

In the last three 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, 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 attend to training activities from GSK, Ferrer, AstraZeneca, and Chiesi.

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REFERENCES

1   Bozek A, Jarzab J. Adherence to Asthma Therapy in Elderly Patients. J Asthma. 2010;47:162–65.

2   Cecere LM, Slatore CG, Uman JE, Evans LE, Udris EM, Bryson CL, et al. Adherence to Long-Acting Inhaled Therapies among Patients with Chronic Obstructive Pulmonary Disease (COPD). COPD J Chronic Obstr Pulm Dis. 2012;9:251–8.

3   Lehmann A, Aslani P, Ahmed R, Celio J, Gauchet A, Bedouch P, et al. Assessing medication adherence: options to consider. Int J Clin Pharm. 2014;36:55–69.

4   Jentzsch NS, Camargos P, Sarinho ESC, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. Respir Med. 2012;106:338–43.

5   Klok T, Kaptein AA, Duiverman EJ, Brand PL. It's the adherence, stupid (that determines asthma control in preschool children)! Eur Respir J. 2013;43:783–91.

6   Toy EL, Beaulieu NU, McHale JM, Welland TR, Plauschinat CA, Swensen A, et al. Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med. 2011;105:435–41.

7   Vestbo J, Anderson JA, Calverley PMA, Celli B, Ferguson GT, Jenkins C, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax. 2009;64:939–43.

8   Enríquez-Matas A, Fernández Rodríguez C, Andrés Esteban E, Fernández Crespo J. Main contributory factors on asthma control and health-related quality of life (QoL) in elderly asthmatics. J Investig Allergol Clin Immunol. 2019;30:0.

9   Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M, ASTRO-LAB group. Asthma inhaler adherence determinants in adults: systematic review of observational data. Eur Respir J. 2015;45:994–1018.

10   Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med 2013;107:1481–90.

11   Rau JL. Determinants of patient adherence to an aerosol regimen. Respir Care 2005 [cited 2018 Apr 30];50:1346–56; discussion 1357-9.

12   Plaza V, López-Viña A, Entrenas LM, Fernández-Rodríguez C, Melero C, Pérez-

Llano L, et al. Differences in Adherence and Non-Adherence Behaviour Patterns to Inhaler Devices Between COPD and Asthma Patients. COPD J Chronic Obstr Pulm Dis. 2016;13:547–54.

13   Normansell R SE. Cochrane Database of Systematic Reviews Interventions to improve adherence to inhaled steroids for asthma (Review) www.cochranelibrary.com DOI: 10.1002/14651858.CD012226.pub2

14   Plaza V, Fernández-Rodríguez C, Melero C, Cosío BG, Entrenas LM, Pérez de Llano L, et al. Validation of the 'Test of the Adherence to Inhalers' (TAI) for asthma and COPD patients. Aerosol Med Pulm Drug Deliv. 2016;29(2):142–52.

15   Plaza V, López-Viña A, Cosio BG: Test of Adherence to Inhalers. Arch Bronconeumol (English Ed). 2017;53:360–1.

16   Busse WW, Lemanske RF: National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma (GINA) Guidelines. Middleton's Allergy Princ Pract. 2009;1743–65.

17   Plaza Moral V. GEMA4.0. Guía española para el manejo del asma. Arch Bronconeumol. 2015;51:2–54.

18   de Llano LP, Sanmartin AP, González-Barcala FJ, Mosteiro-Añón M, Abelaira DC, Quintas RD, et al. Assessing adherence to inhaled medication in asthma: Impact of once-daily versus twice-daily dosing frequency. The ATAUD study. J Asthma. 2018;1–6.

19   Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: http://www.goldcopd.org/ (accessed 23 May, 2016).

20   Jones PW, Brusselle G, Dal Negro RW, Ferrer M, Kardos P, Levy ML, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J. 2011;38:29–35.

21   Vega JM, Badia X, Badiola C, López-Viña A, Olaguíbel JM, Picado C, et al. Validation of the Spanish Version of the Asthma Control Test (ACT). J Asthma. 2007;44:867–72.

22   García-Río F, Calle M, Burgos F, Casan P, del Campo F, Galdiz JB, et al. Espirometría. Arch Bronconeumol. 2013;49:388–401.

23   Roca J, Sanchis J, Agusti-Vidal A, Segarra F, Navajas D, Rodriguez-Roisin R, et al. Spirometric reference values from a Mediterranean population. Bull Eur Physiopathol Respir. [cited 2018 Apr 30];22:217–24.

24   Lasmar L, Camargos P, Champs NS, Fonseca MT, Fontes MJ, Ibiapina C, et al. Adherence rate to inhaled corticosteroids and their impact on asthma control. Allergy. 2009;64:784–9.

25   Carter BL, Foppe van Mil JW. Comparative Effectiveness Research: Evaluating Pharmacist Interventions and Strategies to Improve Medication Adherence. Am J Hypertens. 2010;23:949–55.

26   Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: How unintentional is it really? BMC Health Serv Res. 2012;12:98.

27   Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. 2015;2015:1–12.

28   López-Viña A, Giner J, Molina J, Palicio J, Plaza J, Quintano JA, et al. Multidisciplinary Consensus on the Nonadherence to Clinical Management of Inhaled Therapy in Spanish asthma patients. Clin Ther. 2017;39:1730-1745.e1.

29   Grimm P. Social Desirability Bias. In: Wiley International Encyclopedia of Marketing. Chichester, UK, John Wiley & Sons, Ltd, 2010. DOI: 10.1002/9781444316568.wiem02057

30   Kimberlin CL, Winterstein AG. Validity and reliability of measurement instruments used in research. Am J Heal Pharm. 2008;65:2276–84.

31   Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. Med Care. 2004 [cited 2018 May 26];42:649–52.

32   Brandstetter S, Finger T, Fischer W, Brandl M, Böhmer M, Pfeifer M, et al. Differences in medication adherence are associated with beliefs about medicines in asthma and COPD. Clin Transl Allergy. 2017;7:39.

Figure. Percentage of non-adherent patients according to the 10-item Test of Adherence to Inhalers (50 points) and pharmacy refill records.

Figure
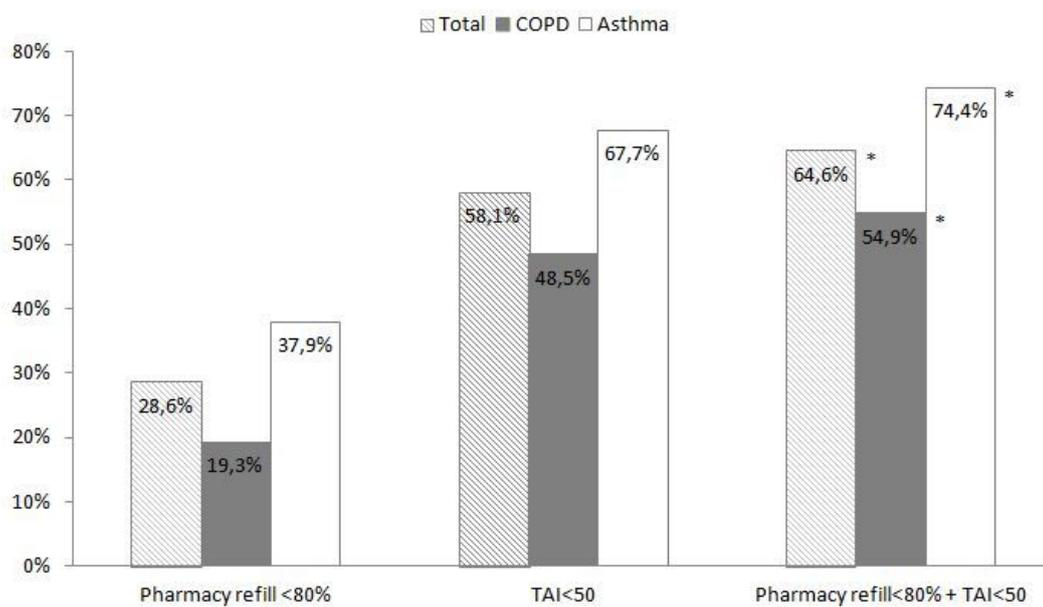
* p<0.001 compared to pharmacy refill <80% and TAI<50.

Table 1. Baseline patient sociodemographic and clinical characteristics

Variable	All patients (n=816)*	Asthma (n=406) *	COPD (n=410)*
Age, years	60.1 (17.2)	49.8 (16.7)	70.2 (10.2)
Sex, male; n (%)	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, n(%)	304 (37)	283 (70)	21 (5)
Received training in inhaler use, n (%)	616 (75.5)	331 (81.5)	285 (69.5)
Proper inhaler technique verified, n (%)	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	n/a	19.3 (4.8)	17.1 (7.6)
Uncontrolled disease (ACT <20 or CAT >10), n(%)	n/a	176 (43.8%)	319 (77.8%)

*All data given as means with SD unless otherwise indicated.
Abbreviations: FEV_1 indicates forced expiratory volume in one second; FVC, forced vital capacity; preBD, pre-bronchodilator testing; postBD, post-bronchodilator testing; ACT, Asthma Control Test; CAT, COPD Assessment Test; n/a, not applicable.

Table 2. Adherence according to TAI and pharmacy refill rate.

	ALL (n=816)	Asthma group (n=406)	COPD group (n=410)	*p* value*
TAI				
Total score, mean (SD)	46.0 (6.0)	45.1 (6.6)	47.0 (5.2)	<0.001
Level of adherence, n (%)				
Good (50 points)	342 (41.9)	131 (32.3)	211 (51.5)	
Intermediate (46-49 points)	234 (28.7)	134 (33.0)	100 (24.4)	<0.001
Poor (≤ 45 points)	240 (29.4)	141 (34.7)	99 (24.1)	
Type of nonadherence, n (%) **				
Erratic	447(45.6)	262 (51.2)	185 (39.5)	<0.001
Deliberate	295 (30.1)	166 (32.4)	129 (27.6)	<0.005
Unwitting	238 (24.3)	84 (16.4)	154 (32.9)	<0.001
PHARMACY REFILL DATA				
Number of devices prescribed in last 6 months, mean (SD)	5.6 (2.3)	5.0 (1.9)	6.3 (2.3)	<0.001
Number of devices filled at the pharmacy in last 6 months, mean (SD)	4.6 (2.3)	3.8 (2.2)	5.4 (2.2)	<0.001
Patients with pharmacy refill rate ≥ 80% last 6 months, n (%>%	583 (71.4)	252 (62.1)	331 (80.7)	<0.001

Abbreviations: TAI indicates Test of Adherence to Inhalers;

*Between asthma and COPD groups. Student's t test or chi-square test, as appropriate.

**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 by TAI and pharmacy refill rate

Patient set	10-item TAI		Bias[1]	Agreement	
PRR	Adherent, n (%)	Non-adherent, n (%)	P value	Observed	Kappa [95% CI]
All Adherent Non-adherent	289 (35.4%) 53 (6.5%)	294 (36.0%) 180 (22.1%)	<0.001	57.5%	0.20 [0.15- 0.26]
Asthma Adherent Non-adherent	104 (25.6%) 27 (6.7%)	148 (36.5%) 127 (31.3%)	<0.001	56.9%	0.21 [0.12- 0.29]
COPD Adherent Non-adherent	185 (45.1%) 26 (6.3%)	146 (35.6%) 53 (12.9%)	<0.001	58.0%	0.15 [0.07- 0.22]
PRR: Pharmacy refill rate; TAI: test of adherence to inhalers; COPD: chronic obstructive pulmonary disease. Adherence based on TAI was defined as TAI=50; Adherence based on PRR was defined as PRR ≥ 80%. [1] McNemar's 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 non-adherence profile)

Mean score on TAI questions 11-12 according to status (yes [scoring 2 points] vs. no [one point]) for inhaler technique training and verification							
		ALL	*P**	ASTHMA	*P**	COPD	*P**
Received inhaler technique training	Yes	3.73 (0.51)	<0.001	3.80 (0.45)	0.016	3.65 (0.56)	<0.001
	No	3.44 (0.70)		3.61 (0.61)		3.33 (0.73)	
Inhaler technique verified	Yes	3.75 (0.50)	<0.001	3.83 (0.40)	<0.001	3.66 (0.58)	<0.001
	No	3.40 (0.69)		3.52 (0.69)		3.32 (0.68)	

*Student's t test

Abbreviations: TAI indicates Test of Adherence to Inhalers; COPD, chronic obstructive pulmonary disease.