



Burden of asthma among patients adherent to ICS/LABA: A real-world study

Jill Davis, Frank Trudo, James Siddall & Mark Small

To cite this article: Jill Davis, Frank Trudo, James Siddall & Mark Small (2018): Burden of asthma among patients adherent to ICS/LABA: A real-world study, Journal of Asthma, DOI: [10.1080/02770903.2018.1455858](https://doi.org/10.1080/02770903.2018.1455858)

To link to this article: <https://doi.org/10.1080/02770903.2018.1455858>



Published online: 06 Apr 2018.



Submit your article to this journal [↗](#)



Article views: 41



View related articles [↗](#)



View Crossmark data [↗](#)



Burden of asthma among patients adherent to ICS/LABA: A real-world study

Jill Davis, MS^a, Frank Trudo, MD^b, James Siddall, BA^c, and Mark Small, BSc^c

^aHealth Economics and Outcomes Research, AstraZeneca, Wilmington, DE, USA; ^bMedical Affairs, AstraZeneca, Wilmington, DE, USA; ^cAdelphi Real World, Adelphi Mill, Bollington, Cheshire, UK

ABSTRACT

Objectives: Asthma is a chronic respiratory condition with a U.S. prevalence of 7.4%. Despite numerous treatment options, asthma remains poorly controlled in some patients. Uncontrolled asthma is associated with high healthcare resource utilization (HCRU) and reduced productivity. This study assessed symptoms, productivity, and HCRU of patients adherent to medium/high-dosage inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) treatment, and the relationship of asthma control with these parameters. **Methods:** Data were collected in the U.S. in 2013–2016 in the Adelphi Respiratory Disease Specific Programme, a cross-sectional survey. Participating physicians ($n = 258$) each completed a record form for eligible patients, who were receiving medium/high-dosage ICS/LABA treatment with self-reported moderate/high adherence, completed the Asthma Control Test (ACT) and the Work Productivity and Activity Impairment (WPAI) questionnaire, and were included in the analyses. **Results:** Patients ($n = 428$) had a mean of 59% symptom-free days in the past month. Wheezing was the most troublesome symptom for 25% of patients. In the previous 12 months, the mean number of exacerbations was 1.3; 15% of exacerbations required emergency room treatment and/or hospitalization. Mean physician visits for asthma was 5.7. Asthma impacted leisure/personal time frequently/constantly for 11% of patients, with 20% overall work impairment. Asthma was poorly controlled (ACT score ≤ 15) in 18% of patients; poorer asthma control was associated with higher rates of exacerbations, work impairment, and HCRU. **Conclusion:** Given the substantial burden described, greater attention to asthma monitoring and management is necessary. Identification of novel treatments may be important for patients not responding to medium/high-dosage ICS/LABA treatment.

ARTICLE HISTORY

Received 11 December 2017
Revised 26 February 2018
Accepted 19 March 2018

KEYWORDS

Asthma control; adherence; healthcare resource utilization; survey; work impairment

Introduction

Asthma is a chronic condition in which episodic and reversible inflammation and narrowing of the bronchi results in recurrent wheezing, chest tightness, shortness of breath, and coughing, with coughing often being the most troublesome at night or early in the morning (1). Asthma attacks and exacerbations can result from exposure to a range of allergens or airborne irritants, exercise, stress, colds or influenza, or extremes of weather (2). The prevalence of asthma in U.S. adults in 2015 has been reported as 7.6% (3), while globally the prevalence has been reported to range from 1% to 16% (4).

Currently available asthma medications include rapid-acting agents used to treat intermittent acute symptoms and exacerbations, and long-term control agents used to achieve and maintain control of persistent asthma. Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach to treatment to address asthma symptom control and risk factors for longer term outcomes (5), as shown in Figure 1. Although for many patients with asthma, disease control can be achieved through

environmental, lifestyle, and therapeutic interventions, not all patients achieve adequate asthma control even with medication (6,7). Poor adherence to medication regimens is a recognized issue in asthma (8); and increasing adherence can often lead to significant improvements in asthma control. However, some patients continue to have poorly controlled asthma even when adherent to high-intensity treatment (9), and represent a much more difficult to treat asthma population given they are not responding to higher daily dosages of inhaled corticosteroids.

Asthma has been reported to be associated with reduced work productivity (10–12). Uncontrolled asthma can result in a high level of healthcare resource utilization (HCRU), including visits to healthcare professionals (HCPs), with unscheduled visits and trips to the emergency room (ER) and hospitalizations not uncommon (10,11).

This analysis assessed the symptom burden, work productivity impact, and HCRU of patients adherent to medium- or high-dosage inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) treatment. In this

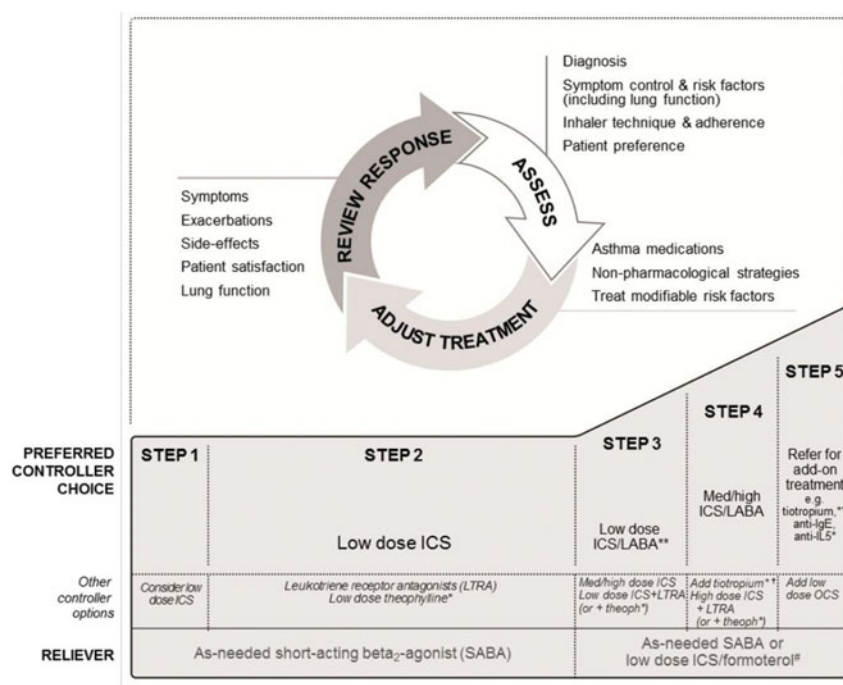


Figure 1. Stepwise approach to asthma treatment. Figure reproduced with permission from Global Initiative for Asthma, 2017b. *Not for children <12 years. **For children 6–11 years, the preferred Step 3 treatment is medium dose ICS. #Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol for maintenance and reliever therapy. †Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years. ICS, inhaled corticosteroids; IgG, immunoglobulin G; IL5, interleukin 5; LABA, inhaled long-acting beta agonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, inhaled short-acting beta agonists.

respect, the adherence of the patient to their treatment has already been established and is unlikely to be a contributing factor to asthma disease burden reported in this study. The relationships between the level of asthma control and the reported symptomatic burden, work impairment, and HCRU were also considered.

Methods

Data collection

Data were taken from the Adelphi Real World Respiratory Disease Specific Programme (DSP), a real-world, point-in-time, patient record-based survey of patients with asthma and chronic obstructive pulmonary disease (COPD). The DSP methodology has been published (13). Data were collected in the U.S. between 2013 and 2016, during which period the DSP was fielded 3 times, in Q4 2013, Q4 2014–Q1 2015, and Q4 2015–Q1 2016.

Physicians were identified from publicly available lists and contacted to complete a telephone screening to determine if they met the entry criteria to be invited to participate in the program. To be included in the DSP, physicians had to be board certified in a primary care (family medicine, internal medicine) or respiratory (pulmonologist, allergist) specialty for at least 5 and no more than 35 years and were required to be managing

patients with asthma and patients with COPD. The data for the current analysis came from the first 5 patients aged over 12 years with a physician-confirmed diagnosis of asthma attending each of the participating physicians' office or clinic; these patients are referred to as the study population. Physicians completed a patient record form (PRF) for each patient, including demographics, asthma diagnosis and medical history, asthma-related HCP consultation history, spirometry test results, details of exacerbations in the previous 12 months, and current and prior treatment information.

Each patient was invited to fill out a patient self-complete form (PSC), which was optional. PSCs collected information on demographics, asthma medical history, current asthma treatment, and details of current asthma symptoms and a standalone question on the impact of asthma on leisure and personal time. The following validated questionnaires were included: Asthma Control Test (ACT) (14), the Work Productivity and Activity Impairment questionnaire (WPAI) (15), and the Morisky Medication Adherence Scale (MMAS) (16).

Study population

Patients were required to have a diagnosis of asthma to be included in the analysis; patients with a physician-confirmed diagnosis of concomitant COPD were

excluded. Patients also had to be currently prescribed medium- or high-dosage ICS/LABA treatment, the parameters of which are defined in Table 1. Only patients with self-reported moderate to high adherence according to the MMAS (see description of MMAS in section on Questionnaires) were included.

Questionnaires

The ACT is a validated 5-question patient-completed questionnaire that asks patients to rate i) impact of asthma at work, school, or home, ii) frequency of shortness of breath, iii) nocturnal symptoms, iv) rescue inhaler usage, and v) patient overall perception of asthma control, with 5 responses per item allocated a score from 1 to 5, resulting in a total score in the range 5–25 (14). Patients with a score of ≤ 15 were defined as poorly controlled, those with a score between 16 and 19 were defined as not well controlled, and those with a score of ≥ 20 were defined as well controlled.

The WPAI questionnaire is designed to measure impairments in both paid work and unpaid everyday activities such as work around the house, shopping, child care, exercising, studying, etc. It consists of 6 questions establishing employment status, hours missed owing to asthma and other reasons, actual number of hours worked, and the degree to which asthma affected productivity and impaired everyday activities on a 0–10 scale (15). Those items related to work were only answered by patients in paid employment while all patients were asked to report their total activity impairment. It results in the generation of 4 scores, each expressed as a percentage of work time missed or a percentage impairment:

- absenteeism (work time missed due to impairment): calculated as hours missed as a percentage of total work hours using: patient-reported hours missed during the 7-day recall period/(patient-reported hours worked during the 7-day recall period + patient-reported hours missed during the 7-day recall period) $\times 100$;
- presenteeism (ability to function at work while being impaired): calculated as a percentage using: patient-reported impact of asthma on productivity

at work during the 7-day recall period recorded on a scale of 0 (no impact) to 10 (prevented me from working) $\times 10$;

- overall work impairment: calculated as a percentage using: patient-reported hours worked, patient-reported hours missed, and patient-reported impact of asthma on productivity during the 7-day recall period, applying an algorithm described on the WPAI website (17); and
- total activity impairment: calculated as a percentage using: patient-reported impact of asthma on productivity in regular unpaid activities during the 7-day recall period recorded on a scale of 0 (no impact) to 10 (prevented activities) $\times 10$.

The MMAS comprises 8 multidimensional items related to intentional and unintentional non-adherence, providing a total score between 0 and 8 (16). Patients with a score of 8 were defined as having high adherence, those with a score of 6 or 7 were defined as having moderate adherence, and those with a score of < 6 were defined as having low adherence and were excluded from the study. The resultant classification provides a qualitative assessment of a patients' adherence to treatment and has been used recently for measuring adherence in asthma patients (18,19).

Analysis

Descriptive statistics were produced for each outcome, with no imputation for missing data. Mean values are presented $\pm$ standard deviations. Patients were grouped by their ACT score and categorized as poorly controlled, not well controlled, or well controlled. Outcomes were evaluated by ACT score category via descriptive statistics.

Ethical considerations

The original research was conducted as a market research survey in accordance with the amended Declaration of Helsinki, adhering to the ICC/ESOMAR International Code on observational research (20), and performed in full accordance with the rules of the U.S. Health Insurance Portability and Accountability Act 1996 (21).

Table 1. Classification of ICS/LABA dosage levels^{a,b}.

Medication	Low dosage	Medium dosage	High dosage
Budesonide/Formoterol fumarate dihydrate (pMDI)	80/4.5 (320 μ g ICS)	Not applicable	160/4.5 (640 μ g ICS) ^c
Fluticasone propionate/Salmeterol xinafoate DPI	100/50 (200 μ g of ICS)	250/50 (500 μ g of ICS)	500/50 (1000 μ g of ICS)
Fluticasone propionate/Salmeterol xinafoate HFA	45/21 (180 μ g of ICS)	115/21 (460 μ g of ICS)	230/21 (920 μ g of ICS)
Fluticasone furoate/Vilanterol	100/25 (100 μ g of ICS)	not applicable	200/25 (200 μ g of ICS)
Mometasone furoate/Formoterol fumarate dihydrate	Not applicable	100/5 (400 μ g of ICS)	200/5 (800 μ g of ICS)

Note. ^aBased on GINA guidelines (GINA 2017). ^bTo be included, patients were required to be currently prescribed medium- or high-dosage ICS/LABA treatment.

^cClassified as medium dosage by GINA but treated as high dosage for the purpose of this study.

DPI, dry powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, inhaled long-acting beta agonists; pMDI, pressurized metered-dose inhaler.

All patients included in the Respiratory DSP provided written informed consent to participate. All data were anonymized and aggregated prior to receipt by Adelphi Real World for analysis.

Results

Study population

Of the 3215 patients with asthma collected from 628 physicians within the observation period in the United States, a total of 428 patients from 258 physicians (106 PCPs, 117 pulmonologists, and 35 allergists) met inclusion criteria and were included in this analysis. One thousand three hundred and eight-one patients were excluded as they declined to complete a self-completion questionnaire. The mean age of the patients was 44 years; 62% were female, 2.4% were smokers, and 70% were employed (Table 2).

Symptomatic burden

The mean forced expiratory volume in one second (FEV₁) reported by physicians was 65.2% ± 19.7% (±SD) of the

predicted normal value among the 240 patients with data available.

The majority (81%) of patients reported experiencing symptoms of asthma. When describing the frequency of symptoms, 31% (130/419) of patients reported experiencing symptoms more than twice a week during the previous 30 days, with 10% reporting symptoms occurring every day (Figure 2A). The mean number of symptom-free days reported out of the past 30 days was 17.8 ± 9.8 (59% of 30 days).

During the previous 4 weeks, the most troublesome symptom was wheezing, which was reported by 25% (64/259) of patients, followed by shortness of breath on exertion, reported by 19% (50/259) of patients (Figure 2B). Overall, 11% of patients (46/414) indicated that asthma symptoms impacted their leisure or personal time frequently or constantly, although 34% reported no impact. (Figure 2C).

Productivity at work

Of the patients with available data included in the analysis, 278 (70%) were currently employed, 29 (7%) were homemakers, and 32 (8%) were students (Table 2). Not all patients completed all relevant items on the WPAI: absenteeism was calculated using data available from 267 patients, presenteeism was calculated using data available from 276 patients, and overall work impairment was calculated using data available from 263 patients. Asthma resulted in considerable work impairment, particularly in terms of presenteeism and overall work impairment. The mean absenteeism, presenteeism, and overall work impairment in the previous 7 days due to asthma were 2.4% ± 9.8%, 18.6% ± 19.1%, and 19.6% ± 20.4%, respectively. Based on an average 40-hour working week, this equates to 7.8, 7.4, and 1.0 hours lost due to overall work impairment, presenteeism, and absenteeism, respectively.

Exacerbations and Health care resource utilization

In the previous 12 months, patients had experienced a mean of 1.3 ± 1.9 asthma exacerbations, with 36% (153/422) of patients having 2 or more exacerbations in this period. Exacerbations were defined as physician-confirmed worsening of symptoms beyond normal day to day variations, although not all exacerbations reported required medication changes or other interventions. However, data gathered on the PRFs indicated that asthma resulted in substantial HCRU.

There was a high level of variability in the number of asthma related HCP visits; the mean numbers of scheduled total physician, primary care, and specialist visits for asthma reported in the previous 12 months were

Table 2. Patient demographics (physician-reported unless stated otherwise).

Parameter	
Age, years – N	428
Mean (SD)	43.9 (16.3)
Female – N	428
n (%)	266 (62.1)
Ethnicity – N	427
Caucasian – n (%)	326 (76.3)
African American – n (%)	59 (13.8)
Hispanic – n (%)	26 (6.1)
Asian, Indian subcontinent – n (%)	2 (0.5)
Asian, Other – n (%)	8 (1.9)
Other – n (%)	6 (1.4)
BMI, kg/m ² – N	405
Mean (SD)	29.5 (6.8)
Smoking status – N	415
Never smoked – n (%)	337 (81.2)
Ex-smoker – n (%)	68 (16.4)
Smoker – n (%)	10 (2.4)
Patient employment status (patient-reported) – N	400
Employed – n (%)	278 (69.5)
Homemaker – n (%)	29 (7.3)
Retired/Unemployed/Long-term disability – n (%)	61 (15.3)
Student – n (%)	32 (8.0)
Selected comorbidities	
CV risk factors (hypertension, hyperlipidemia) – n/N (%)	114/428 (26.6)
Serious CV condition – n/N (%)	210/397 (52.9)
Allergic rhinitis – n/N (%)	132/228 (57.9)
Gastroesophageal reflux disease – n/N (%)	82/428 (19.2)
Anxiety or depression – n/N (%)	94/428 (22.0)

Note. BMI, body mass index; CV, cardiovascular; Serious CV includes angina pectoris, cardiac arrhythmias, congestive heart failure, coronary artery disease, myocardial infarction, peripheral vascular disease, pulmonary arterial hypertension, cerebrovascular disease or thrombosis; SD, standard deviation. Lower denominator for allergic rhinitis as information not collected in 2016 survey.

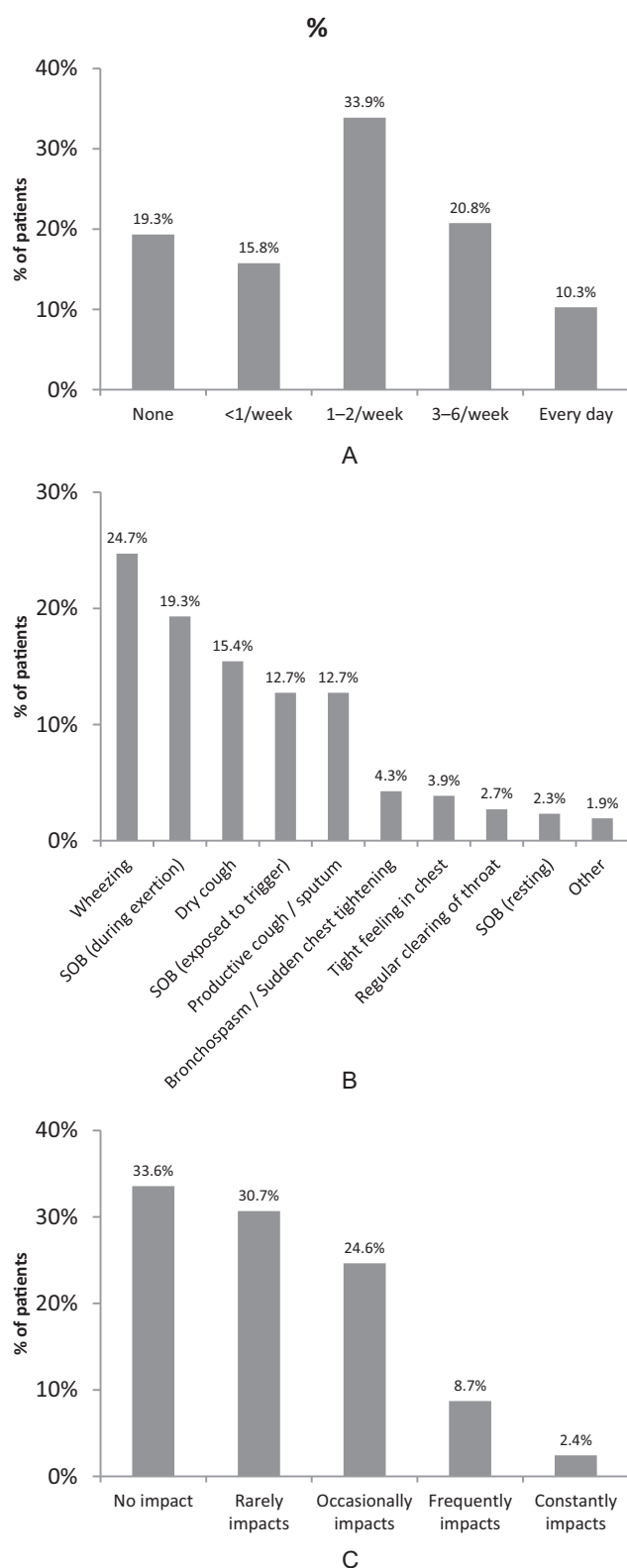


Figure 2. Patient-reported symptomatic burden of asthma: (A) Maximum frequency of symptoms (during previous 30 days); (B) Most troublesome symptoms (during previous 4 weeks); (C) Impact on daily living: leisure/personal time SOB, shortness of breath.

5.7 ± 12.0 , 1.9 ± 3.8 , and 3.4 ± 7.0 , respectively. In addition to these scheduled visits, 15.2% of exacerbations required treatment in the ER and/or involved hospitalization. PRFs included completed hospitalization information for 422 patients; of these, 13% of patients (54/422) had been hospitalized at least once and 2% (8/422) had been hospitalized on 3 or more occasions in the past 12 months as a result of an asthma exacerbation. For those patients admitted to hospital, the mean number of asthma related in-patient days in the previous 12 months was 5.4 ± 7.04 .

Stratification based on asthma control status

The ACT was completed by 403 patients: 199 (49%) were well controlled (ACT score ≥ 20), 130 (32%) were not well controlled (ACT score 16–19), and 74 (18%) were poorly controlled (ACT score ≤ 15). There were substantial associations between asthma control status and medication use, work impairment, frequency of exacerbations, and HCRU in terms of visits to physicians and hospitalizations (Table 3).

Among poorly controlled patients, 73% (54/74) reported using their rescue inhaler at least once daily, compared with 7% (9/130) and 0% (0/199) of not well-controlled patients and well-controlled patients, respectively (Table 3). The mean number of oral corticosteroid (OCS) bursts decreased with increasing levels of control (Table 3), with 50% (34/68) of poorly controlled patients receiving at least 2 OCS bursts within the last 12 months compared with 37% (47/128) and 11% (22/196) of not well-controlled and well-controlled patients, respectively.

Asthma control status was related to productivity at work and in unpaid activities, with the mean absenteeism from work due to asthma in the past 7 days ranging from $9.7\% \pm 15.8\%$ for poorly controlled patients to $0.3\% \pm 2.0\%$ for those who were well controlled. Presenteeism showed a similar relationship with control status; the mean impairment while working due to asthma reported by poorly controlled patients was $41\% \pm 27\%$, while well-controlled patients reported only $8\% \pm 12\%$ presenteeism. The mean overall work impairment due to asthma was $44\% \pm 29\%$, $29\% \pm 14\%$, and $8\% \pm 13\%$ and the mean total activity impairment was $60\% \pm 23\%$, $31\% \pm 14\%$, and $11\% \pm 14\%$, for poorly controlled, not well-controlled, and well-controlled patients, respectively (Table 3).

As might be expected, the mean number of exacerbations experienced in the previous 12 months was correlated with asthma control status (Table 3). Overall, 81% (59/73) of poorly controlled patients experienced at least one exacerbation within the last 12 months

Table 3. Measures of asthma burden and HCRU by level of asthma control.

	Poorly-controlled ^a N = 74	Not well-controlled ^b N = 130	Well-controlled ^c N = 199
Pre-bronchodilator FEV ₁ % predicted ^d , mean	59.1 (n = 39)	53.9 (n = 71)	73.5 (n = 113)
Patients using their rescue inhaler on a daily basis ^e , %	73.0 (n = 74)	6.9 (n = 130)	0.0 (n = 199)
WPAI: % overall work impairment due to asthma ^e , mean	43.7 (n = 30)	28.8 (n = 87)	8.3 (n = 131)
WPAI: % total activity impairment due to asthma ^e , mean	59.9 (n = 70)	31.4 (n = 122)	10.6 (n = 187)
Number of asthma related visits to any physician in the last 12 months ^d , mean	7.47 (n = 74)	6.03 (n = 130)	4.94 (n = 198)
Number of exacerbations ^f in the last 12 months ^d , mean	2.26 (n = 73)	1.48 (n = 127)	0.70 (n = 197)
Number of OCS bursts in the last 12 months ^d , mean	1.78 (n = 68)	1.19 (n = 128)	0.45 (n = 196)
Number of exacerbation-related ER-only visits in the last 12 months ^d , mean	0.63 (n = 73)	0.07 (n = 127)	0.08 (n = 197)
Number of exacerbation-related hospitalizations (ER and admissions) in the last 12 months ^d , mean	0.95 (n = 73)	0.09 (n = 127)	0.09 (n = 197)
Number of asthma related in-patient days in the last 12 months ^d , mean	1.33 (n = 69)	0.04 (n = 125)	0.02 (n = 193)

Note. ^aACT score ≤15; ^bACT score 16–19; ^cACT score ≥20; ^dphysician-reported; ^epatient-reported; ^fany physician-confirmed worsening of symptoms beyond normal day to day variations.

ACT, Asthma Control Test; ER, emergency room; FEV₁, forced expiratory volume in 1 second; OCS, oral corticosteroid; WPAI, Work Productivity and Activity Impairment Questionnaire.

compared with 63% (80/127) and 36% (71/197) of not well-controlled and well-controlled patients, respectively. Three or more exacerbations were reported by 29% (21/73) of poorly controlled patients in the past 12 months, compared with 7% (14/197) of patients who were well controlled.

Well-controlled patients had lower levels of HCRU than less well-controlled patients when considering visits to the ER, hospital admissions, days spent in hospital, and requirement for intensive care (Table 3). Only 6.1% (12/197) of well-controlled patients were hospitalized following an exacerbation in the last 12 months, compared with 7.1% (9/127) and 39.7% (29/73) of not well-controlled patients and poorly controlled patients, respectively. Four poorly controlled patients were hospitalized 5 or more times following an exacerbation in the previous 12 months, while no patients with higher levels of asthma control had this level of hospitalization. The mean number of in-patient days reported was highest in poorly controlled patients and lowest in well-controlled patients. No well-controlled patients were reported as spending time in intensive care in the previous 12 months.

Discussion

Data collected via physician- and patient-reported questionnaires (PRF and PSC, respectively) showed that asthma was associated with substantial symptomatic burden, work impairment, and HCRU. Our findings also showed worsening asthma control was associated with incremental increases in symptoms, absenteeism, presenteeism, and HCRU burden. The burden of difficult-to-treat and severe asthma are well established (6,22,23), but importantly our study findings represent a population of asthma patients who were adherent to their medium- or high-dosage ICS/LABA treatment. Since the most

common cause of uncontrolled asthma is non-adherence to maintenance treatment (24), a sizable proportion of patients in our study are therefore not receiving the expected treatment benefit. It is also a reasonable assumption that outcomes in the equivalent less adherent population would be worse, and therefore asthma control may be achieved by first addressing ways to improve adherence rather than necessarily requiring changes to their treatment.

The findings reported here related to symptomatic burden experienced by patients are comparable to the 12-month Formoterol and Corticosteroids Establishing Therapy (FACET) study. The mean percentages of symptom-free days during the 12-month FACET study of patients with asthma receiving budesonide/formoterol were reported as 51% for patients with a total daily dose of 200 µg budesonide/24 µg formoterol and 55% for patients with a total daily dose of 800 µg budesonide/24 µg formoterol (25), compared with 59% (a mean of 17.8 symptom-free days out of the past 30 days) reported in this study. Our study reported a mean of 1.3 exacerbations of any severity in the previous 12 months in a U.S. study population, with a mean 1.0 requiring acute oral corticosteroid treatment; by contrast, a pooled analysis of 6 open-label international studies of patients with asthma receiving Step 4 budesonide/formoterol treatment reported 0.31 exacerbations per patient per year (26), although patients with a recent exacerbation were excluded.

The level of work impairment due to asthma reported here was similar to that found by Chen et al, who reported 5% absenteeism (compared with 2.4% in this study) and 21% overall work impairment (compared with 20% in this study) (22). This level of productivity impact is comparable with that seen for a number of other diseases. A similar level of absenteeism to that reported in this study has been described for allergic rhinitis, uncontrolled hypertension, and type 2 diabetes (27). A higher level of absenteeism

has been reported for epilepsy (7% in the United States and 9% in Europe) (28) and symptomatic depression (32%) (27). Absenteeism in patients with rheumatoid arthritis has been reported to be similar to that reported in our analysis in some studies (29,30), but has also been reported to be 12–13% in a recent Phase 3 trial (31). Mean presenteeism in our study was much higher than absenteeism, at 19%; presenteeism in the range of 12%–24% has been reported for epilepsy (28), allergic rhinitis, and type 2 diabetes, while it was only 7% for uncontrolled hypertension (27). Presenteeism as high as 49% has been reported for symptomatic depression (27) and 42–46% for rheumatoid arthritis (31). Finally, while overall work impairment as high as 60% has been described for symptomatic depression (27), and close to 30% for epilepsy (27) and allergic rhinitis (27), the 20% reported here is comparable with that seen in type 2 diabetes (27) and in some studies in rheumatoid arthritis (28,30), but higher than that caused by uncontrolled hypertension (27) and other studies in rheumatoid arthritis (31).

The visits to primary care and specialist physicians, as well as ER visits and hospital stays reported here show a substantial utilization of healthcare resources related to asthma, as has been reported elsewhere. In the United States in 2007, 7.2 million visits were made to physician offices and 1.1 million visits to the ER by adults because of asthma and there were 299,000 asthma-related hospitalizations (32). A registry study conducted in North America, Europe, and Asia between 2006 and 2009 (82.1% of patients receiving ICS/LABA with 1675 µg beclomethasone dipropionate equivalent for ICS) reported mean annual unscheduled physician visits related to asthma of 3.8, mean annual ER visits of 1.8, and mean annual hospitalizations of 0.7 (11,33).

The burden of asthma in this study was related to patients' asthma control status, with symptoms, productivity, and HCRU all associated with the level of asthma control. The burden in poorly controlled patients was substantially greater than in patients classified as not well controlled and well controlled, confirming findings previously reported from other studies. In a study using data from the 2006 U.S. National Health and Wellness Survey (34), absenteeism, presenteeism, overall work impairment, visits to healthcare providers, ER visits, and hospitalizations were all observed to be significantly lower in well-controlled patients with an ACT score of ≥ 20 compared to patients with a score of < 20 . A later study, using 2011 data from the same source, confirmed these findings (35).

A number of potential limitations of this study are acknowledged. Firstly, adherence to ICS/LABA treatment was self-reported and could not be verified with pharmacy

claims data. As self-reporting of medication adherence is well documented to be associated with overestimation of medication compliance (36), it is possible that the level of adherence for some patients was actually lower than reported. However, the measure used to assess adherence has been shown to be reliable, with good concurrent and predictive validity in an outpatient setting (16). Secondly, the study population included only patients who consulted a physician and agreed to participate, which could have resulted in a sample that overrepresented patients who visit their physician more frequently than the average patient, or who experience asthma-related symptoms despite adherence to their treatment regimen. Finally, this was a point-in-time study rather than a longitudinal study; thus, descriptive data are presented assessing the association between factors rather than an assessment of causality.

In conclusion, these findings suggest an unmet need in asthma management: patients were still experiencing symptoms and impairment of productivity, and utilizing a considerable level of healthcare resources, despite good adherence to medium- or high-dosage ICS/LABA treatment. Ongoing research is, therefore, essential to better understand all the factors affecting the achievement of asthma control, potentially including identification of novel treatment strategies for patients not responding to ICS/LABA treatment, even at medium- or high-dosage.

Declaration of interest

J Davis and F Trudo hold stock and are employees of AstraZeneca. J Siddall and M Small are employees of Adelphi Real World.

Acknowledgements

The authors wish to thank Thomas Bostock, previously of Adelphi Real World, for his analytical support, and Carole Evans, PhD, of Plan X Consulting (Wirral, Merseyside, UK) for providing medical writing support which was in accordance with Good Publication Practice (GPP3) guidelines and funded by AstraZeneca (Wilmington, Delaware, USA).

Funding

Data collection was undertaken by Adelphi Real World as part of a syndicated survey, entitled the Respiratory Disease Specific Programme, subscribed to by multiple pharmaceutical companies of which one was AstraZeneca. AstraZeneca did not influence the original survey through either contribution to the design of questionnaires or data collection. The analysis described here using data from the Respiratory Disease Specific survey was funded by AstraZeneca and all authors contributed to the analysis and interpretation of the data, the writing of the report and the decision to submit the paper for publication.

References

1. National Institutes of Health. Asthma. 2017. Available at: <https://www.nhlbi.nih.gov/health/health-topics/topics/asthma> [accessed 2017 Nov 14].
2. American College of Allergy, Asthma and Immunology. Asthma information. 2016. Available at: <http://acaai.org/asthma/about> [accessed 2017 Nov 14].
3. National Center for Health Statistics. Asthma. 2017. Available at: <http://www.cdc.gov/nchs/fastats/asthma.htm> [accessed 2017 Nov 14].
4. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention-Online Appendix. 2017a. Available at: <http://ginasthma.org/2017-online-appendix-global-strategy-for-asthma-management-and-prevention> [accessed 2017 Nov 14].
5. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2017b. Available at: <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/> [accessed 2017 Nov 14].
6. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med.* 2006;100:1139–51. doi:10.1016/j.rmed.2006.03.031.
7. Chapman KR, Boulet LP, Rea RM, Franssen E. Suboptimal asthma control: prevalence, detection and consequences in general practice. *Eur Respir J.* 2008;31:320–5. doi:10.1183/09031936.00039707.
8. van Boven JF, Ryan D, Eakin MN, Canonica GW, Barot A, Foster JM, Respiratory Effectiveness Group. Enhancing respiratory medication adherence: the role of health care professionals and cost-effectiveness considerations. *J Allergy Clin Immunol Pract.* 2016;4:835–46. doi:10.1016/j.jaip.2016.03.007.
9. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J.* 2002;19:246–51. doi:10.1183/09031936.02.00218402.
10. Fletcher M, Jha A, Dunlop W, Heron L, Wolfram V, Van der Molen T, Price D. Patient reported burden of asthma on resource use and productivity across 11 countries in Europe. *Adv Ther.* 2015;32:370–80. doi:10.1007/s12325-015-0204-6.
11. Braunstahl GJ, Canvin J, Peachey G, Chen CW, Georgiou P. Healthcare resource utilization in patients receiving omalizumab for allergic asthma in a real-world setting. *Biol Ther.* 2014;4:57–67. doi:10.1007/s13554-014-0019-z.
12. Sadatsafavi M, Rousseau R, Chen W, Zhang W, Lynd L, Fitzgerald JM, Economic Burden of Asthma Study Team. The preventable burden of productivity loss due to suboptimal asthma control: a population-based study. *Chest.* 2014;145:787–93. doi:10.1378/chest.13-1619.
13. Anderson P, Benford M, Harris N, Karavali M, Piercy J. Real-world physician and patient behaviour across countries: Disease-Specific Programmes – a means to understand. *Curr. Med. Res. Opin.* 2008;24:3063–72. doi:10.1185/03007990802457040.
14. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol.* 2004;113:59–65. doi:10.1016/j.jaci.2003.09.008.
15. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics.* 1993;4:353–65. doi:10.2165/00019053-199304050-00006.
16. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich).* 2008;10:348–54. doi:10.1111/j.1751-7176.2008.07572.x.
17. Reilly Associates. WPAI scoring. 2002. Available at: http://www.reillyassociates.net/WPAI_Scoring.html [accessed 2017 Nov 14].
18. Janežič A, Locatelli I, Kos M. Criterion validity of 8-item morisky medication adherence scale in patients with asthma. *PLoS One.* 2017;12(11). Epub 2017 Nov 30. doi.org/10.1371/journal.pone.0187835.
19. Smits D, Brigis G, Pavare J, Maurina B, Barengo NC. Factors related to good asthma control using different medical adherence scales in Latvian asthma patients: an observational study. *NPJ Prim Care Respir Med.* 2017;27:39. Epub 2017 Jun 20. doi:10.1038/s41533-017-0042-x.
20. ICC/ESOMAR. International Code on Market and Social Research. 2007. Available at: https://www.esomar.org/uploads/public/knowledge-and-standards/codes-and-guidelines/ICCESOMAR_Code_English_.pdf [accessed 2017 Nov 15].
21. U.S. Department of Health and Human Services. Summary of the HIPAA Privacy Rule. May 2003. Available at: <http://www.hhs.gov/ocr/privacy/hipaa/understanding/summary/privacysummary.pdf> [accessed 2017 Nov 15].
22. Chen H, Blanc PD, Hayden ML, Bleecker ER, Chawla A, Lee JH, TENOR Study Group. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value Health.* 2008;11:231–9. doi:10.1111/j.1524-4733.2007.00229.x.
23. Al Efraij K, FitzGerald JM. Current and emerging treatments for severe asthma. *J Thorac Dis.* 2015;7(11):E522–5.
24. Lang DM. Severe asthma: epidemiology, burden of illness, and heterogeneity. *Allergy Asthma Proc.* 2015;36(6):418–24. doi:10.2500/aap.2015.36.3908.
25. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International study group. *N Engl J Med.* 1997 Nov 13;337(20):1405–11. doi:10.1056/NEJM199711133372001.
26. Demoly P, Louis R, Söes-Petersen U, Naya I, Carlshamer A, Worth H, Almeida J, Sears MR. Budesonide/formoterol maintenance and reliever therapy versus conventional best practice. *Respir Med.* 2009;103:1623–32. doi:10.1016/j.rmed.2009.07.018.
27. de la Hoz Caballer B, Rodríguez M, Fraj J, Cerecedo I, Antolín-Amérigo D, Colás C. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the Cross-sectional study to evaluate work Productivity in allergic Rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy.* 2012;26:390–4. doi:10.2500/ajra.2012.26.3799.
28. Gupta S, Kwan P, Faught E, Tsong W, Forsythe A, Ryvlin P. Understanding the burden of idiopathic generalized epilepsy in the United States, Europe, and Brazil: an analysis from the National Health and Wellness

- Survey. *Epilepsy Behav.* **2016**;55:146–56. doi: [10.1016/j.yebeh.2015.12.018](https://doi.org/10.1016/j.yebeh.2015.12.018).
29. Hone D, Cheng A, Watson C, Huang B, Bitman B, Huang XY, Gandra SR. Impact of etanercept on work and activity impairment in employed moderate to severe rheumatoid arthritis patients in the United States. *Arthritis Care Res (Hoboken)*. **2013**;65:1564–72.
 30. Stockl KM, Shin JS, Lew HC, Zakharyan A, Harada AS, Solow BK, Curtis BS. Outcomes of a rheumatoid arthritis disease therapy management program focusing on medication adherence. *J Manag Care Pharm.* **2010**;16:593–604.
 31. Keystone EC, Taylor PC, Tanaka Y, Gaich C, DeLozier AM, Dudek A, Zamora JV, Cobos JAC, Rooney T, Bono S, et al. Patient-reported outcomes from a phase 3 study of baricitinib versus placebo or adalimumab in rheumatoid arthritis: secondary analyses from the RA-BEAM study. *Ann Rheum Dis.* **2017 Aug 10**. [Epub ahead of print]. doi:[10.1136/annrheumdis-2017-211259](https://doi.org/10.1136/annrheumdis-2017-211259).
 32. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. *Natl Health Stat Report.* **2011**;12:1–14.
 33. Braunstahl GJ, Chen CW, Maykut R, Georgiou P, Peachey G, Bruce J. The eXpeRience registry: the 'real-world' effectiveness of omalizumab in allergic asthma. *Respir Med.* **2013 Aug**;107(8):1141–51. Epub 2013 May 28. doi:[10.1016/j.rmed.2013.04.017](https://doi.org/10.1016/j.rmed.2013.04.017).
 34. Williams SA, Wagner S, Kannan H, Bolge SC. The association between asthma control and health care utilization, work productivity loss and health-related quality of life. *J Occup Environ Med.* **2009**;51:780–5. doi:[10.1097/JOM.0b013e3181abb019](https://doi.org/10.1097/JOM.0b013e3181abb019).
 35. Vietri J, Burslem K, Su J. Poor asthma control among US workers: health-related quality of life, work impairment, and health care use. *J Occup Environ Med.* **2014**;56:425–30. doi:[10.1097/JOM.0000000000000123](https://doi.org/10.1097/JOM.0000000000000123).
 36. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, Aikens JE, Hunter CM, Veligan DI, Huntley K, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med.* **2015**;5:470–82. doi:[10.1007/s13142-015-0315-2](https://doi.org/10.1007/s13142-015-0315-2).