International Journal of COPD

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Symptomatic burden of COPD for patients receiving dual or triple therapy

This article was published in the following Dove Press journal:
International Journal of COPD

Stephanie Chen[1]
Mark Small[2]
Leandro Lindner[3]
Xiao Xu[1,4]

[1]Health Economics and Payer Analytics, AstraZeneca, Gaithersburg, MD, USA; [2]Respiratory, Adelphi Real World, Bollington, UK; [3]Global Payer Evidence and Pricing, AstraZeneca, Cambridge, UK; [4]Global Payer Evidence and Pricing, AstraZeneca, Gaithersburg, MD, USA

Background: COPD is associated with a large disease burden. The use of dual (two maintenance treatments) and triple (combination of any three treatments) therapy has shown efficacy for symptom relief; however, some patients with COPD remain symptomatic despite these therapies. This study assessed the scope and magnitude of the symptomatic burden for patients with COPD receiving dual or triple therapy.

Patients and methods: Cross-sectional data from three Adelphi COPD surveys (2013–2016) conducted in the USA, Europe, Japan, and China were analyzed for patients with COPD and forced expiratory volume in 1 second ≤65% receiving dual or triple therapy for ≥3 months. Physicians completed clinical and disease characteristic forms for identified patients. Corresponding patients completed questionnaires that included validated survey instruments to assess adherence and symptom impact. Descriptive statistics are reported.

Results: Our analysis included 690 patients (mean age 68.2 years; 73.3% male); 41.4% and 58.6% were receiving dual and triple therapy, respectively. Most patients had dyspnea with substantial disability (modified Medical Research Council dyspnea scale rating ≥2, 56.3%; large health status impairment from symptoms, COPD Assessment Test score >20, 64.4%). A large symptom burden was observed, even for patients highly adherent to treatment (Morisky Medication Adherence Scale 8, 30.3% [185/612]), of whom 62.1% still had a COPD Assessment Test score >20. Sensitivity analyses of patients regardless of their forced expiratory volume in 1 second status and of those receiving treatment for >6 months both reported similar results.

Conclusion: Although patients who consult their physicians more frequently than average may be overrepresented because of the observational design of this study, we report that unmet needs remain for patients with COPD, despite the use of dual or triple therapy. A percentage of patients with COPD reported major symptom burden affecting their daily living and causing a large impairment in the health status, regardless of treatment adherence.

Keywords: COPD, burden of illness, triple therapy, dual therapy

Introduction

COPD is associated with a large disease burden. An estimated 328 million people worldwide have COPD,[1] and the day-to-day impact of the disease can be debilitating for these patients. COPD is associated with significant health care costs of $18 billion annually in the USA, and globally it accounts for 29.4 million years lost because of disability.[1]

The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines grade the severity of COPD based on spirometry assessment to assess the severity of airflow limitation and use criteria based on symptoms and exacerbations in the previous year to estimate the risk of future exacerbations.[2] GOLD recommends assessment of symptoms, including cough and/or sputum production, by using validated

Correspondence: Stephanie Chen
AstraZeneca, 1 MedImmune Way, Gaithersburg, MD 20878, USA
Tel +1 301 398 2598
Email stephanie.chen@astrazeneca.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/COPD.S163717

patient questionnaires, such as the COPD Assessment Test (CAT) or the modified Medical Research Council (mMRC) dyspnea scale.[2] This symptom assessment and history of exacerbations (which are indicative of symptom worsening) are important factors for predicting deterioration in lung function and likelihood of future exacerbations.

Either a short- or long-acting bronchodilator is the initial treatment option for relief of breathlessness for patients with COPD, with a long-acting bronchodilator recommended for patients with more persistent symptoms.[2] Dual therapy (any combination of two maintenance treatments, including inhaled corticosteroids [ICS], long-acting β_2-agonists [LABA], or long-acting muscarinic antagonists [LAMA]) is recommended for patients with persistent breathlessness on monotherapy, and triple therapy (any combination of ICS, LABA, and LAMA) is recommended for patients who develop further exacerbations while on dual therapy.[2] Both dual and triple therapy treatment regimens have been shown to improve the symptoms of patients with COPD.[2,3] However, some patients receiving dual or triple therapy report still suffering from a considerable symptom burden that adversely affects their health-related quality of life (HRQOL) and leads to increased morbidity.[4] For these patients, currently available medications may not be sufficient to provide relief from symptoms or to stabilize disease.

The aim of this study was to further assess the symptom burden of patients with COPD who were receiving dual or triple therapy. We sought to provide evidence of burden of disease in a real-world clinical setting to further characterize the current symptom burden and unmet treatment need for patients with COPD from Europe, Japan, China, and the USA.

Patients and methods

For these analyses, we used data from the Adelphi Real World Respiratory Disease Specific Programme (DSP).[5] DSP is a real-world, point-in-time, patient record–based survey. The DSP provides impartial observations of real-world clinical practice from a physician and matched-patient viewpoint, and is an established method for investigating multicenter patient characteristics and treatment practices for common chronic diseases. DSPs in respiratory disease were conducted in Quarter 4 (Q4) 2013, Q4 2014/Quarter 1 (Q1) 2015, and Q4 2015/Q1 2016. The Respiratory DSPs collected information from patients diagnosed with COPD who were consulting their health care professionals for routine care.

The primary objective of this study was to assess the symptom burden of patients with COPD who were receiving dual or triple therapy and had a forced expiratory volume in 1 second (FEV_1) <65%. Exploratory objectives included assessments for patients with low, moderate, or high treatment adherence and those with differing levels of lung function and length of dual or triple treatment.

All patients included in the Respiratory DSP provided written informed consent to participate. Because this study was a retrospective analysis of secondary data, we had no access to any medical or other patient records or to data sources containing patient or participating physician information. All patient management and treatment choices were at the discretion of the physician, and no tests or measurements were performed as part of the survey.

Ethical approval

The DSP was conducted as a survey that adhered to market research guidelines and the international code of conduct for observational research from the International Chamber of Commerce/European Society for Opinion and Marketing Research.[6] Therefore, ethical approval was not necessary to obtain and was not sought. Patients provided informed consent to participate in the survey via a tick box on the front of the patient self-completion questionnaire. All data were anonymized and aggregated prior to receipt by Adelphi Real World.

DSP survey population

Primary care physicians and pulmonologists were qualified to participate in the Respiratory DSP if they were responsible for treatment of patients with COPD, qualified as a medical doctor 5–35 years ago, and saw ≥3 patients with COPD per month.

Study population

A pooled data set from the three surveys was created to analyze cross-sectional data related to patient characteristics of a large, robust study population. Patients from Europe (France, Germany, Italy, Spain, and the UK), Japan, China, and the USA were included. The following inclusion criteria were used to select patients for the primary study population: physician-confirmed diagnosis of COPD; physician-recorded post-bronchodilator FEV_1 ≤65% predicted (this requirement was removed in sensitivity analysis); and currently prescribed dual therapy (any combination of two maintenance treatments, including ICS, LABA, or LAMA) or triple therapy (any combination of ICS, LABA, and LAMA) for ≥3 months. Patients declining to complete a patient self-completion questionnaire were excluded from

the analysis to limit the amount of missing information for the study population.

Study variables and analysis

Participating physicians completed patient record forms for five consecutive consultations with patients with COPD. Physicians recorded demographics; clinical characteristics, such as exacerbation history; and treatment information. Patients completed disease-related questionnaires, including a patient self-completion questionnaire (detailing the nature of symptoms and the impact on daily activities), and the following validated questionnaires: Morisky Medication Adherence Scale 8 (MMAS-8),[7–9] CAT,[10] mMRC dyspnea scale,[11] and Jenkins Sleep Evaluation Questionnaire (JSEQ).[12] The MMAS-8 consists of eight items that provide a score from 0 to 8; patient adherence to treatment is classified as low (<6), moderate (6–7), or high (8).[7] The CAT patient-reported outcome is an established tool for monitoring COPD. It consists of eight items, each with a 6-point differential scale that produces a score from 0 to 40. A higher score indicates a more severe impact of COPD on the patient's life.[10] The mMRC dyspnea scale consists of five statements about the impact of breathlessness and results in a grade from 0 to 4, where grade 0 equates to the patient experiencing breathlessness only during strenuous exercise and grade 4 equates to the patient being too breathless to leave the house/breathless when dressing.[11] An mMRC ≥2 is associated with a moderate to severe level of dyspnea. The JSEQ consists of four statements regarding sleep disturbance, which patients score by the frequency of experience; total scores range from 0 (no sleep disturbance) to 20 (22–28 days of disturbed sleep for all four statements).[12]

Each variable was described using the maximum available sample size; therefore, sample sizes varied from one variable to another, depending on the quantity of missing data. All analyses were conducted by the Adelphi Real World statistical department using Stata 14.2 or later.[13] All code and result files were saved and are replicable. Descriptive statistics (univariate and bivariate) were used to examine symptom burden across a range of symptom-related characteristics.

Sensitivity analysis

In addition to the overall population, patient characteristics and symptom burden were also assessed for patients categorized by GOLD ABCD group (defined by exacerbation risk and CAT score)[2] to provide characterization based on symptoms and exacerbation risk, together with categorization based on treatment adherence (determined by the MMAS-8 score). Patients with COPD on dual or triple therapy regardless of FEV_1 status and those with FEV_1 ≤65% receiving dual or triple therapy for a minimum of 6 months were also assessed.

Results

Study population

During the observation period (2013–2016), 7,094 patients were diagnosed with COPD and completed a patient self-completion questionnaire. Of these patients, 690 met the inclusion criteria for the primary study population. The main reason for exclusion was missing lung function data/FEV_1 >65% (n=4,121); other patients were excluded because they had not been on dual or triple therapy for >3 months or they had missing duration data. Corresponding information relating to these patients was provided by 436 physicians. Removal of the inclusion criteria for FEV_1 resulted in a population of 2,954 patients.

The mean age of the primary study population was 68.2 years; 73.3% were male, and 26.4% were current smokers (Table 1). Most patients had one or more comorbidity (74.8%). Cardiovascular conditions were the most common concomitant condition; 64.6% of patients had concomitant hypertension (Table 1). Most patients were under a pulmonologist's care (77.1%; Table 1).

In the population of patients with COPD on dual or triple therapy for a minimum of 3 months regardless of FEV_1 status, patient characteristics were similar to those of the primary study population (Table 1). The study population with FEV_1 ≤65% and on dual or triple therapy for a minimum of 6 months was also similar to the primary study population (Table 1).

Treatment

In the primary study population, 41.4% and 58.6% of patients were on dual and triple therapy, respectively (Table 1). ICS/LABA (fixed-dosage combination) was the most common dual therapy (41.6%) and ICS/LABA plus LAMA was the most common triple therapy (88.9%) prescribed to patients. The percentages of patients receiving triple therapy in each of the GOLD ABCD categories were as follows: group A, 35.7%; group B, 50.4%; group C, 83.3%; and group D, 66.6%.

For the sensitivity analysis populations, 52.9% and 47.1% of the overall population regardless of the FEV_1 status were receiving dual and triple therapy, respectively. Of patients with FEV_1 ≤65% on treatment for ≥6 months, 41.3% and 58.7% were receiving dual and triple therapy, respectively (Table 1).

Table 1 Patient demographics and baseline clinical characteristics

	Primary study population (n=690)	Study population, no FEV_1 criteria (n=2,954)	Study population, dual/triple therapy ≥6 months (n=606)
Mean age, years (SD)	68.2 (8.9)	67.1 (9.5)	68.3 (8.8)
Sex, n (%)			
Male	506 (73.3)	2,034 (68.9)	169 (27.9)
Race, n (%)	n=688	n=2,943	n=604
White	602 (87.5)	2,440 (82.9)	538 (89.1)
African American	16 (2.3)	64 (2.2)	10 (1.7)
Hispanic/Latino	18 (2.6)	72 (2.4)	14 (2.3)
Others	52 (7.6)	367 (12.4)	42 (7.0)
Body mass index, kg/m^2 group, n (%)	n=658	n=2,838	n=574
<25	249 (37.8)	1,093 (38.5)	212 (36.9)
25–<27	129 (19.6)	587 (20.7)	116 (20.2)
27–<30	145 (22.0)	619 (21.8)	131 (22.8)
30+	135 (20.5)	539 (19.0)	115 (20.0)
Mean time since diagnosis, months (SD)	n=623	n=2,640	n=548
	77 (66.7)	68.5 (64.2)	77 (66.9)
Current therapy grouping, n (%)	n=690	n=2,954	n=606
Dual	286 (41.4)	1,564 (52.9)	250 (41.3)
Triple	404 (58.6)	1,390 (47.1)	356 (58.7)
Dual therapy combinations, n (%)	n=286	n=1,564	n=250
LABA+LAMA	80 (28.0)	302 (19.3)	74 (29.6)
LABA/LAMA fixed-dosage combination	16 (5.6)	54 (3.5)	48 (19.2)
ICS+LABA	7 (2.4)	30 (1.9)	7 (2.8)
ICS/LABA fixed-dosage combination	119 (41.6)	894 (57.2)	107 (42.8)
ICS+LAMA	64 (22.4)	284 (18.2)	14 (5.6)
Triple therapy combinations ICS/LABA/LAMA ± others, n (%)	n=404	n=1,390	n=356
ICS+LABA/LAMA	12 (3.0)	34 (2.4)	9 (2.5)
ICS/LABA+LAMA	359 (88.9)	1,282 (92.2)	318 (89.3)
LABA+ICS+LAMA	33 (8.2)	74 (5.3)	29 (8.1)
ICS dosage (grouped), n (%)[a]	n=463	n=2,026	n=416
Low	114 (24.6)	554 (27.3)	108 (26.0)
Medium	191 (41.3)	862 (42.5)	168 (40.4)
High	158 (34.1)	610 (30.1)	140 (33.7)
Physician responsible for treatment decisions, n (%)	n=689	n=2,951	n=605
Pulmonologist only	465 (67.5)	1,546 (52.4)	407 (67.3)
Primary care physician only	149 (21.6)	1,079 (36.6)	133 (22.0)
Primary care physician+pulmonologist	66 (9.6)	298 (10.1)	56 (9.3)
Other	9 (1.3)	28 (0.9)	9 (1.5)
MMAS-8, n (%)	n=613	n=2,616	n=539
Low, <6	209 (34.1)	936 (35.8)	180 (33.4)
Moderate, 6–7	219 (35.7)	845 (32.3)	193 (35.8)
High, 8	185 (30.2)	835 (31.9)	166 (30.8)
Mean post-bronchodilator FEV_1, % predicted (SD)	n=690	n=1,379	n=606
	50.27 (11.6)	63.49 (16.4)	49.94 (11.7)
Exacerbations experienced in last 12 months, mean (SD)	n=670	n=2,880	n=587
	1.6 (1.6)	1.3 (1.5)	1.6 (1.6)
Smoking status, n (%)	n=666	n=2,869	n=584
Ex-smoker	465 (69.8)	1,824 (63.6)	154 (26.4)
Current smoker	176 (26.4)	780 (27.2)	406 (69.5)
Has never smoked	25 (3.8)	265 (9.2)	24 (4.1)
Cardiovascular conditions, n (%)	n=642	n=2,714	n=564
Any	503 (78.3)	1,987 (73.2)	444 (78.7)
Hypertension	415 (64.6)	1,636 (60.3)	366 (64.9)
Elevated cholesterol/hyperlipidemia	214 (33.3)	833 (30.7)	184 (32.6)

(*Continued*)

Table 1 (*Continued*)

	Primary study population (n=690)	Study population, no FEV_1 criteria (n=2,954)	Study population, dual/triple therapy ≥6 months (n=606)
Concomitant conditions ≥5% of patients, n (%)	n=620	n=2,666	n=546
Diabetes	129 (20.8)	463 (17.4)	114 (20.9)
Depression	92 (14.8)	301 (11.3)	81 (14.8)
Gastroesophageal reflux disease	84 (13.5)	330 (12.4)	76 (13.9)
Prostate disorder	79 (12.7)	289 (10.8)	67 (12.3)
Anxiety	72 (11.6)	323 (12.1)	66 (12.1)
Obesity	72 (11.6)	253 (9.5)	64 (11.7)
Arthritis	61 (9.8)	312 (11.7)	60 (11.0)
Osteoporosis	53 (8.5)	198 (7.4)	48 (8.8)
Sleep apnea	39 (6.3)	105 (3.9)	33 (6.0)
Dyspepsia/stomach pain	37 (6.0)	162 (6.1)	34 (6.2)

Notes: [a]Low, 100–250 μg fluticasone; medium, >250–500 μg fluticasone; high, >500 μg fluticasone. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; LAMA, long-acting muscarinic antagonists; MMAS-8, Morisky Medication Adherence Scale 8.

Treatment adherence

In the primary study population, 613 patients had completed MMAS-8; 185 patients were highly adherent to treatment (30.2%). The mean age of patients highly adherent to treatment was 67.4 years; 72.4% were male, 26.8% were current smokers, and 68% suffered from concomitant hypertension. These patient characteristics were similar to those of the overall patient population.

Timing of symptoms and frequency of reliever usage

In the primary study population, symptoms occurred most frequently during winter (91.7%) and autumn (62.0%) months (Table 2). Of these patients, 56.7% reported that their symptoms occurred mainly during daytime hours, whereas 38.5% of other patients had equal daytime and nighttime occurrences. Use of a reliever inhaler at least once a week was reported by 67.1% of patients. Patients with greater maintenance medication adherence tended to use their reliever inhaler less frequently than those with lower adherence (Table 3). However, of patients with high adherence, 59.4% still reported using their reliever at least once a week and 33.3% used a reliever inhaler three to six times a week or every day.

Symptom burden

In the primary study population, 45.1% were dissatisfied with their treatment but considered that they were receiving the best possible control that they could, and 11.1% were dissatisfied but believed that better control was possible (Table 2).

Shortness of breath during exertion/exercise was the most common troublesome symptom reported by patients (52.3%; primary study population) during the preceding 4 weeks. Many patients reported experiencing a constant lack of energy (44.9%), tiredness through lack of sleep (30.6%), and were scared or worried about their own condition (31.1%; Table 2). More than half of the patients also reported that COPD at least occasionally affected their leisure/personal time (69.8%) and work (55.9% [if in work]; Table 2). Physician-reported perceived impact of COPD on the patient's HRQOL results was similar to that self-reported by patients (Table 4), as was the one reported by patients in the study population, regardless of the FEV_1 status or duration of treatment (Table 2). In the high–treatment adherence category, 58.9% of patients also reported that they experienced shortness of breath during exertion/exercise as their most common symptom experienced in the previous 4 weeks and that they experienced a constant lack of energy (42.2%).

More than half of the patients in the primary study population had CAT scores >20 (64.4%; Table 2; Figure 1) from a possible total score of 40, indicating a large or very large impact of COPD on the patient's health status.[14] More than 50% of patients had mMRC dyspnea scale scores ≥2, indicating that many patients suffer a degree of breathlessness.[15] The mean JSEQ score was 6.1 out of a possible total score of 20, indicative of experiencing sleep disturbance (Table 2).[12] Similar results were observed for the study population, regardless of the FEV_1 level or duration of treatment (Table 2). For patients categorized by GOLD ABCD group, >50% of patients in GOLD groups B and D had CAT

Table 2 Patient-reported symptom burden and health-related quality of life (patient self-completion questionnaire assessed)

	Primary study population	Study population, no FEV_1 criteria	Study population, dual/triple therapy for ≥6 months
Time of day of symptoms, n (%)	n=671	n=2,871	n=589
Daytime only	103 (15.4)	451 (15.7)	84 (14.3)
Primarily daytime	277 (41.3)	1,283 (44.7)	250 (42.4)
Equally day and night	258 (38.5)	939 (32.7)	227 (38.5)
Primarily nighttime	29 (4.3)	183 (6.4)	25 (4.2)
Nighttime only	4 (0.6)	15 (0.5)	3 (0.5)
Time of year of symptoms, n (%)	n=424	n=1,742	n=375
Spring	143 (33.7)	553 (31.7)	130 (34.7)
Summer	124 (29.2)	424 (24.3)	115 (30.7)
Autumn	263 (62.0)	1,015 (58.3)	235 (62.7)
Winter	389 (91.7)	1,525 (87.5)	341 (90.9)
Most troublesome symptom in the past 4 weeks, n (%)	n=623	n=2,557	n=551
No symptoms	1 (0.2)	14 (0.5)	1 (0.2)
Shortness of breath when resting	78 (12.5)	233 (9.1)	67 (12.2)
Shortness of breath during exertion/exercise	326 (52.3)	1,165 (45.6)	291 (52.8)
Shortness of breath when exposed to trigger	14 (2.2)	61 (2.4)	13 (2.4)
Wheezing	28 (4.5)	138 (5.4)	25 (4.5)
Productive cough/sputum	95 (15.2)	510 (19.9)	81 (14.7)
Dry cough	20 (3.2)	171 (6.7)	18 (3.3)
Coughing up blood	2 (0.3)	20 (0.8)	2 (0.4)
Regular clearing of throat	7 (1.1)	45 (1.8)	7 (1.3)
A tight feeling in the chest	34 (5.5)	119 (4.7)	31 (5.6)
Bronchospasm/sudden chest tightening	18 (2.9)	81 (3.2)	15 (2.7)
Impact of COPD on getting up and ready for the day, n (%)	n=674	n=2,877	n=591
No impact	95 (14.1)	640 (22.2)	81 (13.7)
Rarely impacts	164 (24.3)	826 (28.7)	143 (24.2)
Occasionally impacts	243 (36.1)	901 (31.3)	218 (36.9)
Frequently impacts	137 (20.3)	402 (14.0)	118 (20.0)
Constantly impacts	35 (5.2)	108 (3.8)	31 (5.2)
Impact of COPD on personal relationships, n (%)	n=668	n=2,855	n=585
No impact	101 (15.1)	613 (21.5)	90 (15.4)
Rarely impacts	194 (29.0)	983 (34.4)	169 (28.9)
Occasionally impacts	242 (36.2)	892 (31.2)	212 (36.2)
Frequently impacts	103 (15.4)	300 (10.5)	89 (15.2)
Constantly impacts	28 (4.2)	67 (2.3)	25 (4.3)
Impact of COPD on leisure/personal time, n (%)	n=663	n=2,843	n=581
No impact	53 (8.0)	370 (13.0)	47 (8.1)
Rarely impacts	147 (22.2)	778 (27.4)	127 (21.9)
Occasionally impacts	248 (37.4)	1,035 (36.4)	219 (37.7)
Frequently impacts	168 (25.3)	546 (19.2)	146 (25.1)
Constantly impacts	47 (7.1)	114 (4.0)	42 (7.2)
Impact of COPD on work (if in work), n (%)	n=145	n=740	n=120
No impact	28 (19.3)	171 (23.1)	22 (18.3)
Rarely impacts	36 (24.8)	264 (35.7)	33 (27.5)
Occasionally impacts	53 (36.6)	218 (29.5)	48 (40.0)
Frequently impacts	24 (16.6)	73 (9.9)	16 (13.3)
Constantly impacts	4 (2.8)	14 (1.9)	1 (0.8)
Impact of COPD on sleep, n (%)	n=668	n=2,845	n=585
No impact	116 (17.4)	577 (20.3)	103 (17.6)
Rarely impacts	198 (29.6)	976 (34.3)	174 (29.7)
Occasionally impacts	221 (33.1)	877 (30.8)	195 (33.3)
Frequently impacts	110 (16.5)	356 (12.5)	93 (15.9)
Constantly impacts	23 (3.4)	59 (2.1)	20 (3.4)

(*Continued*)

Table 2 (*Continued*)

	Primary study population	Study population, no FEV_1 criteria	Study population, dual/triple therapy for ≥6 months
Satisfaction with current control of COPD, n (%)	n=506	n=2,198	n=441
Satisfied	222 (43.9)	1,225 (55.7)	201 (45.6)
Dissatisfied, best possible control	228 (45.1)	773 (35.2)	196 (44.4)
Dissatisfied, better control possible	56 (11.1)	200 (9.1)	44 (10.0)
Feelings experienced, n (%)	n=666	n=2,878	n=585
Constant lack of energy	299 (44.9)	1,043 (36.2)	266 (45.5)
Tiredness through lack of sleep	204 (30.6)	857 (29.8)	178 (30.4)
Sickness	48 (7.2)	258 (9.0)	33 (5.6)
Nervousness or anxiety	179 (26.9)	681 (23.7)	155 (26.5)
Feelings of sadness or depression	134 (20.1)	409 (14.2)	117 (20.0)
Difficulty expressing your feelings	63 (9.5)	215 (7.5)	54 (9.2)
Embarrassment about your condition	125 (18.8)	390 (13.6)	110 (18.8)
Scared and worried about your condition	207 (31.1)	719 (25.0)	180 (30.8)
Feelings of irritability	164 (24.6)	625 (21.7)	145 (24.8)
None of them	124 (18.6)	709 (24.6)	109 (18.6)
Reliever inhaler usage, n (%)	n=654	n=2,785	n=572
I am not prescribed a reliever inhaler	42 (6.4)	392 (14.1)	38 (6.6)
Not at all	74 (11.3)	442 (15.9)	67 (11.7)
Less than once a week	99 (15.1)	467 (16.8)	84 (14.7)
Once or twice a week	191 (29.2)	657 (23.6)	175 (30.6)
3–6 times a week	111 (17.0)	379 (13.6)	95 (16.6)
Every day	137 (20.9)	448 (16.1)	113 (19.8)
Modified Medical Research Council dyspnea scale, n (%)	n=650	n=2,755	n=568
I only get breathless with strenuous exercise (grade 0)	64 (9.8)	492 (17.9)	56 (9.9)
I get short of breath when hurrying on level ground or walking up a slight hill (grade 1)	220 (33.8)	1,076 (39.1)	196 (34.5)
On level ground, I walk slower than people of the same age because of my breathlessness, or have to stop for breath when walking at my own pace (grade 2)	206 (31.7)	734 (26.6)	179 (31.5)
I stop for breath after walking for a few minutes on level ground (grade 3)	114 (17.5)	338 (12.3)	98 (17.3)
I am too breathless to leave the house or I am breathless when dressing (grade 4)	46 (7.1)	115 (4.2)	39 (6.9)
COPD Assessment Test, mean (SD)	n=648	n=2,768	n=569
	23.1 (7.9)	21.2 (8.0)	22.9 (7.7)
COPD Assessment Test (grouped), n (%)	n=648	n=2,768	n=569
0–9	43 (6.6)	254 (9.2)	36 (6.3)
10–20	188 (29.0)	971 (35.1)	175 (30.8)
21–30	298 (46.0)	1,213 (43.8)	261 (45.9)
>30	119 (18.4)	330 (11.9)	97 (17.0)
Jenkins Sleep Evaluation Questionnaire, mean (SD)	n=628	n=2,580	n=559
	6.1 (5.0)	5.4 (4.6)	6.0 (5.0)

Abbreviation: FEV_1, forced expiratory volume in 1 second.

scores >20 (57.9% and 78.5%, respectively) and >50% of patients in GOLD group D had mMRC dyspnea scale scores ≥2 (Table 5).

Although there was some improvement in patient burden with increased medication adherence in the primary study population, substantial burden remained for patients who were most adherent. More than half of these patients (64.2%) had a CAT score >20 (Table 3; Figure 1) and 54.2% had an mMRC dyspnea scale score of ≥2 (Table 3).

Discussion

The results of this analysis, using data collected via physician- and patient-reported questionnaires, highlight the large symptom burden experienced by patients with COPD.

Table 3 Symptom burden and health-related quality of life by MMAS-8 (primary study population)

MMAS-8	Physician reported			Patient reported		
	Low (n=209)	Moderate (n=219)	High (n=185)	Low (n=209)	Moderate (n=219)	High (n=185)
Impact of COPD on getting up and ready for the day, n (%)	n=209	n=219	n=185	n=205	n=217	n=183
No impact	17 (8.1)	33 (15.1)	22 (11.9)	22 (10.7)	29 (13.4)	30 (16.4)
Rarely impacts	64 (30.6)	56 (25.6)	43 (23.2)	59 (28.8)	51 (23.5)	40 (21.9)
Occasionally impacts	68 (32.5)	66 (30.1)	68 (36.8)	74 (36.1)	79 (36.4)	63 (34.4)
Frequently impacts	46 (22.0)	55 (25.1)	42 (22.7)	39 (19.0)	46 (21.2)	40 (21.9)
Constantly impacts	14 (6.7)	9 (4.1)	10 (5.4)	11 (5.4)	12 (5.5)	10 (5.5)
Impact of COPD on personal relationships, n (%)	n=208	n=216	n=184	n=207	n=214	n=179
No impact	16 (7.7)	23 (10.6)	37 (20.1)	25 (12.1)	30 (14.0)	29 (16.2)
Rarely impacts	71 (34.1)	80 (37.0)	49 (26.6)	54 (26.1)	66 (30.8)	58 (32.4)
Occasionally impacts	79 (38.0)	65 (30.1)	72 (39.1)	78 (37.7)	71 (33.2)	70 (39.1)
Frequently impacts	34 (16.3)	44 (20.4)	21 (11.4)	38 (18.4)	37 (17.3)	18 (10.1)
Constantly impacts	8 (3.8)	4 (1.9)	5 (2.7)	12 (5.8)	10 (4.7)	4 (2.2)
Impact of COPD on leisure/personal time, n (%)	n=208	n=218	n=185	n=204	n=213	n=180
No impact	6 (2.9)	13 (6.0)	14 (7.6)	14 (6.9)	10 (4.7)	16 (8.9)
Rarely impacts	45 (21.6)	48 (22.0)	47 (25.4)	44 (21.6)	53 (24.9)	41 (22.8)
Occasionally impacts	84 (40.4)	72 (33.0)	63 (34.1)	76 (37.3)	81 (38.0)	67 (37.2)
Frequently impacts	58 (27.9)	70 (32.1)	49 (26.5)	56 (27.5)	50 (23.5)	44 (24.4)
Constantly impacts	15 (7.2)	15 (6.9)	12 (6.5)	14 (6.9)	19 (8.9)	12 (6.7)
Impact of COPD on work (if in work), n (%)	n=44	n=41	n=37	n=47	n=41	n=41
No impact	6 (13.6)	5 (12.2)	5 (13.5)	9 (19.1)	8 (19.5)	9 (22.0)
Rarely impacts	10 (22.7)	14 (34.1)	11 (29.7)	7 (14.9)	13 (31.7)	12 (29.3)
Occasionally impacts	12 (27.3)	13 (31.7)	16 (43.2)	21 (44.7)	11 (26.8)	15 (36.6)
Frequently impacts	14 (31.8)	6 (14.6)	3 (8.1)	8 (17.0)	7 (17.1)	5 (12.2)
Constantly impacts	2 (4.5)	3 (7.3)	2 (5.4)	2 (4.3)	2 (4.9)	0 (0.0)
Impact of COPD on sleep, n (%)	n=208	n=218	n=184	n=207	n=215	n=180
No impact	21 (10.1)	39 (17.9)	40 (21.7)	29 (14.0)	38 (17.7)	37 (20.6)
Rarely impacts	70 (33.7)	75 (34.4)	59 (32.1)	63 (30.4)	62 (28.8)	54 (30.0)
Occasionally impacts	67 (32.2)	67 (30.7)	59 (32.1)	68 (32.9)	76 (35.3)	59 (32.8)
Frequently impacts	43 (20.7)	32 (14.7)	23 (12.5)	38 (18.4)	31 (14.4)	26 (14.4)
Constantly impacts	7 (3.4)	5 (2.3)	3 (1.6)	9 (4.3)	8 (3.7)	4 (2.2)
Satisfaction with current control of COPD, n (%)				n=145	n=158	n=148
Satisfied				56 (38.6)	66 (41.8)	78 (52.7)
Dissatisfied, best possible control				66 (45.5)	81 (51.3)	58 (39.2)
Dissatisfied, better control possible				23 (15.9)	11 (7.0)	12 (8.1)
Feelings experienced, n (%)				n=206	n=216	n=180
Constant lack of energy				90 (43.7)	102 (47.2)	76 (42.2)
Tiredness through lack of sleep				72 (35.0)	65 (30.1)	45 (25.0)
Sickness				20 (9.7)	15 (6.9)	6 (3.3)
Nervousness or anxiety				64 (31.1)	62 (28.7)	41 (22.8)
Feelings of sadness or depression				49 (23.8)	47 (21.8)	31 (17.2)
Difficulty expressing your feelings				28 (13.6)	17 (7.9)	12 (6.7)
Embarrassment about your condition				41 (19.9)	51 (23.6)	29 (16.1)
Scared and worried about your condition				67 (32.5)	73 (33.8)	49 (27.2)
Feelings of irritability				64 (31.1)	50 (23.1)	37 (20.6)
None of them				27 (13.1)	41 (19.0)	50 (27.8)
Reliever inhaler usage, n (%)				n=203	n=208	n=180
I am not prescribed a reliever inhaler				9 (4.4)	15 (7.2)	15 (8.3)
Not at all				10 (4.9)	30 (14.4)	29 (16.1)
Less than once a week				26 (12.8)	32 (15.4)	29 (16.1)
Once or twice a week				76 (37.4)	52 (25.0)	47 (26.1)
3–6 times a week				39 (19.2)	28 (13.5)	29 (16.1)
Every day				43 (21.2)	51 (24.5)	31 (17.2)
Modified Medical Research Council dyspnea scale, n (%)				n=199	n=210	n=175
I only get breathless with strenuous exercise (grade 0)				17 (8.5)	21 (10.0)	20 (11.4)
I get short of breath when hurrying on level ground or walking up a slight hill (grade 1)				66 (33.2)	72 (34.3)	60 (34.3)

(*Continued*)

Table 3 (*Continued*)

MMAS-8	Physician reported			Patient reported		
	Low (n=209)	Moderate (n=219)	High (n=185)	Low (n=209)	Moderate (n=219)	High (n=185)
On level ground, I walk slower than people of the same age because of my breathlessness, or have to stop for breath when walking at my own pace (grade 2)				64 (32.2)	61 (29.0)	57 (32.6)
I stop for breath after walking for a few minutes On level ground (grade 3)				43 (21.6)	31 (14.8)	27 (15.4)
I am too breathless to leave the house or I am breathless when dressing (grade 4)				9 (4.5)	25 (11.9)	11 (6.3)
COPD Assessment Test				n=201	n=210	n=179
Mean (SD)				23.0 (7.8)	23.9 (7.8)	22.9 (7.7)
COPD Assessment Test (grouped), n (%)				n=201	n=210	n=179
0–9				9 (4.5)	13 (6.2)	15 (8.4)
10–20				58 (28.9)	67 (31.9)	49 (27.4)
21–30				93 (46.3)	85 (40.5)	94 (52.5)
>30				41 (20.4)	45 (21.4)	21 (11.7)
Jenkins Sleep Evaluation Questionnaire, mean (SD)				n=194	n=201	n=174
				6.8 (5.2)	6.3 (5.1)	4.9 (4.5)

Notes: Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.
Abbreviation: MMAS-8, Morisky Medication Adherence Scale 8.

Table 4 Physician-reported symptom burden and health-related quality of life (patient record form assessed)

	Primary study population	Study population, no FEV_1 criteria	Study population, dual/triple therapy ≥6 months
Impact of COPD on getting up and ready for the day, n (%)	n=690	n=2,951	n=606
No impact	85 (12.3)	647 (21.9)	73 (12.0)
Rarely impacts	186 (27.0)	945 (32.0)	161 (26.6)
Occasionally impacts	224 (32.5)	823 (27.9)	201 (33.2)
Frequently impacts	157 (22.8)	429 (14.5)	136 (22.4)
Constantly impacts	38 (5.5)	107 (3.6)	35 (5.8)
Impact of COPD on personal relationships, n (%)	n=683	n=2,876	n=600
No impact	94 (13.8)	631 (21.9)	87 (14.5)
Rarely impacts	225 (32.9)	1,037 (36.1)	192 (32.0)
Occasionally impacts	237 (34.7)	834 (29.0)	206 (34.3)
Frequently impacts	107 (15.7)	326 (11.3)	97 (16.2)
Constantly impacts	20 (2.9)	48 (1.7)	18 (3.0)
Impact of COPD on leisure/personal time, n (%)	n=688	n=2,946	n=604
No impact	38 (5.5)	335 (11.4)	34 (5.6)
Rarely impacts	158 (23.0)	882 (29.9)	135 (22.4)
Occasionally impacts	246 (35.8)	998 (33.9)	219 (36.3)
Frequently impacts	200 (29.1)	609 (20.7)	174 (28.8)
Constantly impacts	46 (6.7)	122 (4.1)	42 (7.0)
Impact of COPD on work (if in work), n (%)	n=136	n=744	n=114
No impact	18 (13.2)	153 (20.6)	17 (14.9)
Rarely impacts	38 (27.9)	275 (37.0)	32 (28.1)
Occasionally impacts	44 (32.4)	203 (27.3)	37 (32.5)
Frequently impacts	28 (20.6)	95 (12.8)	23 (20.2)
Constantly impacts	8 (5.9)	18 (2.4)	5 (4.4)
Impact of COPD on sleep, n (%)	n=687	n=2,921	n=603
No impact	116 (16.9)	640 (21.9)	105 (17.4)
Rarely impacts	229 (33.3)	1,103 (37.8)	195 (32.3)
Occasionally impacts	210 (30.6)	817 (28.0)	189 (31.3)
Frequently impacts	115 (16.7)	318 (10.9)	100 (16.6)
Constantly impacts	17 (2.5)	43 (1.5)	14 (2.3)

Abbreviation: FEV_1, forced expiratory volume in 1 second.

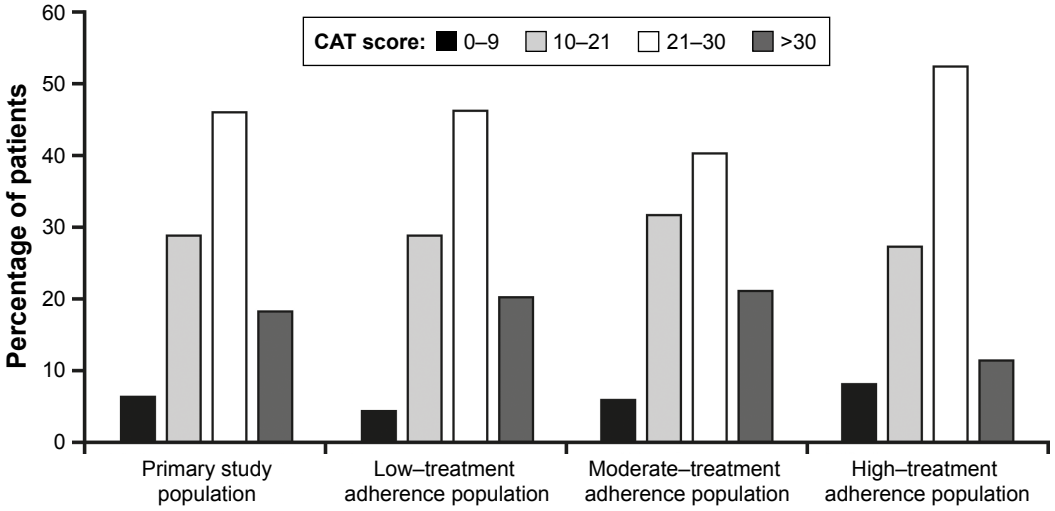

Figure 1 Percentage of patients by CAT score category for the primary study population overall and by adherence to treatment categories.[a]
Notes: [a]Assessed using the MMAS-8: low, <6; moderate, 6–7; high, 8. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.
Abbreviations: CAT, COPD Assessment Test; MMAS-8, Morisky Medication Adherence Scale 8.

The use of dual and triple therapy treatment has been associated with clinically meaningful improvements in lung function and HRQOL and reduced exacerbations in patients with COPD.[2,3] However, we found that despite receiving dual or triple therapy, some patients with COPD and FEV_1 ≤65% reported a significant burden of symptoms that affected their everyday lives. This symptom burden was also significant in those with good treatment adherence. More than half of this patient population presented with CAT scores >20 (64.4%) and mMRC dyspnea scale scores ≥2 (56.3%). This large symptom burden was experienced by patients regardless of their lung function and by those who had been receiving treatment for a minimum of 6 months.

Previous studies examining the burden of symptoms for patients with moderate/severe COPD have reported similar results to our findings, such as approximately half of the patients having an mMRC dyspnea scale score ≥2 and associated greater CAT score.[16,17] However, these studies

Table 5 Symptom burden of patients categorized by GOLD ABCD group

	Overall[a] (N=640)	GOLD group[2]			
		A (n=28)	B (n=268)	C (n=15)	D (n=329)
CAT score	N=640	n=28	n=268	n=15	n=329
Mean (SD)	23.1 (7.9)	6.3 (2.5)	21.9 (6.4)	7.1 (2.0)	26.2 (6.4)
0–9, n (%)	43 (6.7)	28 (100.0)	0 (0)	15 (100.0)	0 (0)
10–20, n (%)	184 (28.7)	0 (0)	113 (42.2)	0 (0)	71 (21.6)
21–30, n (%)	294 (45.9)	0 (0)	128 (47.8)	0 (0)	166 (50.5)
>30, n (%)	119 (18.6)	0 (0)	27 (10.1)	0 (0)	92 (28.0)
mMRC dyspnea scale, n (%)	n=610	n=27	n=255	n=12	n=316
I only get breathless with strenuous exercise (grade 0)	59 (9.7)	16 (59.3)	26 (10.2)	3 (25.0)	14 (4.4)
I get short of breath when hurrying on level ground or walking up a slight hill (grade 1)	206 (33.8)	8 (29.6)	108 (42.4)	6 (50.0)	84 (26.6)
On level ground, I walk slower than people of the same age because of my breathlessness, or have to stop for breath when walking at my own pace (grade 2)	194 (31.8)	2 (7.4)	80 (31.4)	3 (25.0)	109 (34.5)
I stop for breath after walking for a few minutes on level ground (grade 3)	107 (17.5)	1 (3.7)	35 (13.7)	0 (0)	71 (22.5)
I am too breathless to leave the house or I am breathless when dressing (grade 4)	44 (7.2)	0 (0)	6 (2.4)	0 (0)	38 (12.0)
JSEQ score, n	n=589	n=27	n=244	n=13	n=305
Mean (SD)	6.0 (5.0)	1.1 (2.0)	4.9 (4.4)	1.1 (1.4)	7.6 (5.1)

Note: [a]Overall GOLD group.
Abbreviations: CAT, COPD Assessment Test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; JSEQ, Jenkins Sleep Evaluation Questionnaire; mMRC, Modified Medical Research Council.

have often been limited to national data or evaluation of a limited number of symptoms.[16–19] Uniquely, this study used treatment as a criterion for analyses of symptom burden applied to a worldwide patient population. The findings highlight the large unmet need for further treatments for symptom control in patients with COPD, whose disease significantly affects their daily lives despite receiving current standard-of-care therapy for severe disease. The disease characteristics and symptom burden for the secondary study populations (those without an FEV_1 inclusion criterion and those who had been on medication for a minimum of 6 months) were similar to those of the primary study population. These similarities demonstrate that the large burden of symptoms for patients with COPD is not restricted to those with reduced lung function, those with suboptimal adherence to treatment, or those who have been on dual or triple therapy for <6 months.

In this study population, symptoms occurred most frequently during daytime hours and the autumn and winter months. These results are consistent with previous studies. The ASSESS study reported that despite regular treatment, 90.5% of patients with stable COPD experienced symptoms at some point during the day,[20] while the TORCH long-term international study demonstrated an increased risk of COPD exacerbations in the winter months in northern (Canada, China, 26 eastern and western European countries, and the USA) and southern (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa) regions.[21] Our results on the prevalence of daytime/nighttime symptoms, breathlessness being the most common symptom, prevalence of sleep impairment, and more than half of patients being dissatisfied with their current medications' ability to control symptoms were in general agreement with previous studies.[4,17]

Previous studies have reported that concordance of symptom burden and impact on HRQOL reports from physicians and patients are greater for patients with more severe COPD compared with those with milder disease.[21] In our study, there was reasonable concordance between physician- and patient-reported responses describing symptom burden, suggesting that physician–patient communication is not a barrier to improving care for patients with more severe disease, although it may be a factor for those with milder disease.

The data used in this study were collected from patients consulting their physicians in a routine care setting with no excessively restrictive exclusion criteria and, therefore, are representative of patients in a real-world clinical setting. However, this study has some potential limitations. Patients who consulted a physician and agreed to participate were included in the study; therefore, patients who consulted their physician more frequently or who were experiencing COPD-related symptoms may be overrepresented in the study population. Furthermore, the impact of undertreatment on symptom burden could not be evaluated and the focus of this study was symptom burden, and exacerbation rate was not included; therefore, only one dimension of the clinical burden was considered for patients with COPD. For these reasons, generalizability of our findings to the whole COPD population may be limited. It is also not known to what extent those patients who did not complete a patient self-completion questionnaire (and were therefore excluded from the analysis) differed from those who did complete the questionnaire; this circumstance may introduce a further bias of patient selection. In addition, the quality of data is dependent on accurate reporting of information by physicians and patients, although physicians were permitted to use patient records to limit errors in actual treatment, events, and comorbidities. As part of sensitivity analyses, the GOLD ABCD classification system was used to categorize patients based on their degrees of symptom burden and exacerbation risk. However, the timing of classification, whether at diagnosis or subsequent evaluations, may be subject to interpatient variation. Other limitations include the cross-sectional retrospective study design. Our report assessed associations between factors and did not identify causality, and retrospective reports of adverse events were not provided. We also did not assess the effect of patients receiving double or triple therapy on their symptom burden, which may further limit the interpretation of our results.

Conclusion

Despite receiving dual or triple therapy, a number of patients with COPD still reported major symptoms that affected their everyday lives and impaired their health status. For patients with COPD receiving dual or triple therapy, we found associations between symptomatic burden and adherence to treatment. Nevertheless, some highly adherent patients still had substantial symptom burden. Further research is necessary to identify novel treatment strategies for patients who continue to experience symptoms despite receiving dual or triple treatment regimens.

Acknowledgments

This analysis was funded by AstraZeneca. We wish to thank Tom Bailey and Megan Scott for their contributions to this work. Editorial support was provided by Debra Scates, PhD, of JK Associates, Inc. and Michael A Nissen, ELS, of AstraZeneca. This support was funded by AstraZeneca.

Disclosure

Mark Small is an employee of Adelphi Real World. Stephanie Chen, Leandro Lindner, and Xiao Xu are employees of AstraZeneca. The authors report no other conflicts of interest in this work.

References

1. Lopez-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology*. 2016;21(1):14–23.
2. GOLD [webpage on the Internet]. GOLD 2018 Global Strategy for the Diagnosis, Management and Prevention of COPD. Available from: http://goldcopd.org/gold-reports/. Accessed March 20, 2018.
3. Tabberer M, Lomas DA, Birk R, et al. Once-daily triple therapy in patients with COPD: patient-reported symptoms and quality of life. *Adv Ther*. 2018;35(1):56–71.
4. Singh D, Miravitlles M, Vogelmeier C. Chronic obstructive pulmonary disease individualized therapy: tailored approach to symptom management. *Adv Ther*. 2017;34(2):281–299.
5. 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(11):3063–3072.
6. ICC/ESOMAR. International Code on Market and Social Research 2007. Available from: https://www.esomar.org/uploads/public/knowledge-and-standards/codes-and-guidelines/ICCESOMAR_Code_English_.pdf. Accessed November 7, 2017.
7. 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(5):348–354.
8. Morisky DE, DiMatteo MR. Improving the measure of self-reported medication nonadherence: final response. *J Clin Epidemiol*. 2011;64(3):258–263.
9. Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. *Am J Manag Care*. 2009;15(1):59–66.
10. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648–654.
11. Williams N. The MRC breathlessness scale. *Occup Med (Lond)*. 2017;67(6):496–497.
12. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol*. 1988;41(4):313–321.
13. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. [Computer program] 2015.
14. Ghobadi H, Ahari SS, Kameli A, Lari SM. The relationship between COPD Assessment Test (CAT) scores and severity of airflow obstruction in stable COPD patients. *Tanaffos*. 2012;11(2):22–26.
15. Stenton C. The MRC breathless scale. *Occup Med (Lond)*. 2008;58(3):226–227.
16. Henoch I, Strang S, Lofdahl CG, Ekberg-Jansson A. Health-related quality of life in a nationwide cohort of patients with COPD related to other characteristics. *Eur Clin Respir J*. 2016;3:31459.
17. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. *Respir Res*. 2017;18(1):67.
18. Joshi M, Joshi A, Bartter T. Symptom burden in chronic obstructive pulmonary disease and cancer. *Curr Opin Pulm Med*. 2012;18(2):97–103.
19. Ding B, DiBonaventura M, Karlsson N, Bergstrom G, Holmgren U. A cross-sectional assessment of the burden of COPD symptoms in the US and Europe using the National Health and Wellness Survey. *Int J Chron Obstruct Pulmon Dis*. 2017;12:529–539.
20. Miravitlles M, Worth H, Soler Cataluna JJ, et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. *Respir Res*. 2014;15:122.
21. Jenkins CR, Celli B, Anderson JA, et al. Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur Respir J*. 2012;39(1):38–45.