OBSERVATIONAL STUDY REPORT SYNOPSIS

Symptoms and Physical Activity in COPD patients in Europe (SPACE study)

An observational, multinational, cross sectional study to describe 24-hours symptoms, physical activity and their relationship in stable COPD patients in Europe

Milestones:	**First Subject In: 21-Dec-2016** **Last Subject In: 31-Aug-2017**
Phase of development:	Not Applicable – Observational study
Sponsor:	AstraZeneca
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This study was performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice, including the archiving of essential documents.

Study centres:

Approximately 144 centres in 11 countries: Austria, Belgium, Bulgaria, Greece, Israel, Netherlands, Poland, Portugal, Romania, Serbia, and Slovakia.

Background/Rationale:

Chronic Obstructive Pulmonary Disorder (COPD) is a common disease associated with significant morbidity and mortality, despite its preventable and treatable character. [1] The characteristic symptoms are worsening dyspnea, exercise limitation, and progressive deterioration of health status. [2] Respiratory symptoms of COPD have a considerable degree of variation for the same level of airflow limitation and can significantly impact the patients' quality of life. [1, 3, 4]

Physical activity is closely related to autonomy in self-care, ambulation and overall physical functioning. Physical activity limitations constitute an important consequence of the respiratory impairment caused by COPD, being a major contributor of the decreased quality of life. [1, 5, 6]

To the best of our knowledge, no study evaluated the frequency and severity of COPD symptoms over a period of 24-hours (e.g., night-time, morning and day-time symptoms) and patterns of physical activity in stable COPD patients in different healthcare settings from Europe. The correlation between (i) respiratory symptoms experienced during night-time, morning and day-time and (ii) physical activity patterns and specific outcomes such as GOLD ABCD classification, adherence to maintenance respiratory treatment, level of dyspnea, disease severity, comorbidities and quality of life will be additionally explored. COPD treatment patterns in different European healthcare systems will be also described.

In 2011, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has proposed the combined assessment of airflow limitation (FEV1), symptoms and exacerbations history, resulting in four groups (A/B/C/D). [7] This assessment has been in use until the most recent update of GOLD, launched in December 2016. The GOLD recommendations for 2017 include a FEV1-free approach of the ABCD groups, stratifying patients only by symptoms assessment and exacerbation history. [1] Following these recommendations, SPACE study will describe the study population by both old and new ABCD classification criteria, exploring thus their implications on the disease management decisions.

Objectives:

Primary objective:

To describe prevalence and severity of early morning, day and night-time symptoms as well as patterns of physical activity in patients with stable COPD in several European countries.

Secondary objectives:

To evaluate the relationship between (1) early morning, day and night-time symptoms and (2) patterns of physical activity, and the following items:

- Exacerbation history in previous 12 months
- Adherence to respiratory treatment
- Disease GOLD 2013 and GOLD 2017 classification, severity (BODEx), level of dyspnoea (mMRC), comorbidities (COTE)
- HRQoL (CAT)
- Direct Cost of disease (Healthcare Resource Use – HRU in past 12 months and medication costs in last 2 months without any change)

Additional objectives:

1. To describe COPD treatments in Europe according to therapeutic class and modality of use (rescue *vs.* maintenance)
2. To describe the classification of COPD patients by GOLD 2013 and GOLD 2017 assessment tool

No formal hypotheses testing will be performed.

Study design:

This was a multi-country, multicentre, non-interventional, cross-sectional study in patients with stable COPD from several European countries. The study had one single study visit.

Data source(s):

To determine eligibility, site staff has reviewed patients' medical records. Patients with a formal spirometric diagnosis and stable COPD have been screened and, if considered eligible and expressed consent for study participation, enrolled.

For each patient, Investigators have collected data from medical records or during clinical interview: socio-demographics, lifestyle, health-insurance system, smoking history, comorbidities, level of dyspnoea, disease severity, exacerbation history, healthcare resource utilisation, and COPD treatments (rescue and maintenance) in the last 2 months before study visit. At study visit, patients have been asked to provide data on disease-related symptomatology assessed over the last 24-hours, adherence to treatment, health-related quality of life (HRQoL) and physical activity.

Study population: Patients enrolled in the study had stable COPD according to 2013 GOLD criteria. A total number of 2190 patients from 144 centres were enrolled in the study, and 2162 patients were included in the final study analysis.

Inclusion Criteria:

1. Male or female patient aged 40 years or older
2. Patient has a diagnosis of COPD for 1 year or more
3. Patient has at least one spirometry with COPD criteria fixed ratio <0.70 post-BD in previous 12 months
4. Patient is a current smoker of an ex-smoker with a smoking history of ≥10 pack-years
5. Stable patient, as stated in medical records or patient reports during visit, defined as: without exacerbation treatment at study visit neither in the previous 2 months and without changes in COPD maintenance treatment regimen over the preceding 2 months (avoid first consult patients)
6. Patient must be able and willing to read and comprehend written instructions, and comprehend and complete the questionnaires required by the protocol
7. After full explanation, patient has signed an informed consent document indicating that he understands the purpose of and the procedures required for the study and is willing to participate in the study

Exclusion criteria:

1. Patient has a diagnosis of sleep apnoea syndrome or other chronic respiratory disease different from chronic obstructive diseases (except for non-idiopathic pulmonary fibrosis and ACOS, only if the main diagnosis is COPD)
2. An acute or chronic condition that, in the investigator's opinion, would limit the patient's ability to complete questionnaires or to participate in this study
3. Patient is participating in an on-going clinical trial that might, in the investigator's opinion to influence the assessment for SPACE study

Statistical methods:

Statistical analyses are of explorative and descriptive nature. The standard descriptive statistics for continuous variables include N, mean ± SD if normally distributed or median ± IQR if non-normally distributed, minimum and maximum. The standard descriptive statistics for categorical variables include N and percentage (%).

To test the differences in means or medians of continuous variables between two groups, t-test has been used for normally distributed variables, and Wilcoxon signed rank test for non-normally distributed variables, respectively. To analyse the mean differences between more than two groups, one-way analysis of variance or Kruskal-Wallis Rank Sum test have been used. To test the difference between the expected frequencies and the observed frequencies in one or more categories, Chi-square has been employed.

To test the relationship between two variables, correlation analysis has been employed, and either Pearson or Spearman correlation coefficient has been used based on the distribution of variables. As deemed necessary, regression analyses (linear or logistic) have been applied to identify the relationship between a dependent variable and one or more independent variables. To assess the agreement of 2013 and 2017 GOLD classification tool, Cohen's kappa coefficient has been calculated. These two classification tools have been also compared on their association with symptoms and physical activity levels. Z score transferred by Fisher's r-to-z transformation has been applied to test of the equality of two correlation coefficients obtained from the same sample, with the two correlations sharing one variable in common.

All analyses will be also applied to subgroups by country and provided separately to each country.

All tests are two-sided. P-value ≤0.05 has been considered statistically significant.

Results:

Demographic, anthropometric and social characteristics

A total number of 2162 patients with mean (±SD) age of 66.86 (±8.40) years were included in the final analysis, the majority of whom were male (70%). Most patients (94.2%) were insured in the public healthcare system and a high percentage (81.1%) was retired.

Disease characteristics and medical history

More than half of the patients (63.2%) had confirmed CV diseases, with hypertension the most frequent CV disease reported in 54.8% patients. A total number of 159 patients (7.4%) had a previous diagnosis of asthma, and for 179 (8.3%) of patients, various types of cancer were reported. Mean COTE index (±SD) was 1.47 (±2.23).

The mean duration (±SD) of COPD was 7.4 (±5.8) years. The median score of mMRC was 2 and a total number of 1401 (64.8%) patients had dyspnea assessed on the mMRC scale as grade ≥2. The mean score of CAT (±SD) was 16.52 (7.94). Overall, 1335 (61.75%) patients presented exacerbations in previous year, with a mean number (±SD) of moderate COPD exacerbations of 0.61 (±1.15) and a mean number (±SD) of severe COPD exacerbations of 0.22 (±0.64) in the previous year. The mean BODEx index (±SD) was 2.62 (±1.79).

Healthcare resource utilization

The mean number (±SD) of COPD-related visits to the general practitioner or family doctor in the previous year was 4.36 (±7.31). The mean number (±SD) of COPD-related visits to the pulmonology or internal medicine specialist in the previous year was 3.23 (±5.21)

COPD treatments per therapeutic class and COPD patterns in Europe

A total number of 2139 (98.94%) patients received treatment of any class.

Overall, the most common types of maintenance treatment were LAMA alone (51.4%), combined LABA+ICS (51.3%) and combined LABA+LAMA (23.5%). In the LAMA alone group (e.g. LAMA in one separate inhaler, not in inhalers containing LAMA in combination with other substances) the highest usage at country level was in Serbia in 75.2% of patients, followed by the Netherlands (67.8%) and Bulgaria (61.4%). Portugal and Romania had the lowest usage of LAMA alone with 33.1% and 34.5% of patients, respectively. In the group of combined LABA + ICS, the highest usage at country level was observed in Bulgaria (79.0%), Serbia (66.4%) and the Netherlands (60.3%), while Portugal and Slovakia presented the lowest usage in 27.7% and 30.0% of patient, respectively. The highest usage of the LAMA + LABA combination was described in Portugal (61.5%), Austria (46.4%) and Slovakia (46%). The lowest usage of LAMA + LABA was observed in Serbia (0.4%). Further data about the usage in each country for the complete list of COPD medication classes is detailed in Table 16.1

From the 77 treatment patterns used by SPACE study participants, the most frequent pattern consisted of triple therapy with LAMA + LABA + ICS, irrespective of the rescue medication and other maintenance medication associated (e.g., mucolytics, methylxantines etc). In total, 41% of patients received triple therapy with different combinations of LAMA + LABA + ICS,

where LAMA + LABA + ICS only (without any other maintenance treatment associated) was administered in 25.4% patients in FAS. At country level, the Netherlands has had the highest usage of LAMA + LABA + ICS only in 52.9% of patients as compared to Romania, which had the lowest usage in 9.4%. The second most reported pattern consisted of LABA + LAMA in different combinations in 22.6% of patients, with 19% patients in FAS receiving LAMA + LABA only (combination without any other maintenance treatment associated). At country level, LAMA + LABA only was most commonly used in Slovakia in 40% of patients as compared to Serbia in 2.8% patients. LABA + ICS was the third combination most frequently administered in 19.4% patients, with 14.2 % of patients overall receiving LABA + ICS only (combination without any other maintenance treatment associated). At country level LABA + ICS combination only was used in 26.1% patients in Romania as compared to 2.9% in Austria. LAMA alone (monotherapy associated or not with other maintenance treatments) was administered in 9.6% of patients, with monotherapy exclusively in 8% of patients. Serbia had the highest usage of LAMA monotherapy in 16.8% patients as compared to the Netherlands, with the lowest usage in 3.3% patients.

Adherence to respiratory treatment

The analysis of Investigator's assessment of the inhaler's technique for maintenance treatments indicated a correct technique for 76.7% of patients. Poor technique was assessed in 1.6% of patients.

More than half of the patients (67.6%) estimated a very good to excellent ability in taking the daily regular respiratory medication during the last month, as assessed through SRSI.

GOLD 2013 & GOLD 2017 disease classification

The proportion of patients categorised into groups A to D differed according to the use of a GOLD symptom cut-point of mMRC grade ≥2 or CAT score ≥10 for each edition of guideline (2013 and 2017). When GOLD 2013 classification was applied, mMRC classified 46.6% patients in the group D, compared with 55% with the CAT. When GOLD 2017 classification was applied, mMRC classified 29.4% patients in the group D, compared with 36.2% with the CAT.When the groups of high symptoms were combined (e.g., B + D), the percentages remained the same, irrespective of the GOLD edition considered, and differed only by the questionnaires used: both mMRC GOLD 2013 and GOLD 2017 classified 64.8% patients as having high symptoms (groups B and D), compared with 79.6% with CAT GOLD 2013 and GOLD 2017.

A high degree of agreement was described between the different editions of the GOLD recommendations when (i) the same questionnaire was used (either mMRC or CAT) and (ii) when the concordance was assessed within the same edition of GOLD recommendations.

Prevalence and severity of respiratory symptoms over 24-hrs

The mean RS-Total Score (±SD) in FAS was 11.33 (±7.50). The mean NiSCI Overall COPD Severity domain score (±SD) in FAS was 0.72 (±0.91), and the mean EMSCI Overall COPD

Severity domain score (±SD) in FAS was 1.14 (±0.89). The symptoms severity calculated using the 6-items severity score and overall COPD symptoms severity scores for both NiSCI and EMSCI correlated strongly (Pearson's product correlation r=0.77, with P<0.001 for both).

In each part of the day, patients have presented symptoms. Daytime and early morning symptoms were most common: 93.43% of patients presented at least one day-time symptom, 85.25% presented at least one early morning (evaluated using the 6-item domain) and 70.26% patients presented at least one symptom during the night (evaluated using the 6-item domain).

Cough was the most frequently reported symptom in the early morning (68.59% of patients), followed by dyspnea (64.94%). A similar pattern was seen during the daytime, when cough was the most prevalent symptom (79.32% of patients), followed by dyspnea (71.74%). The most frequently reported symptom during the night was dyspnea (50.51%) followed by cough (45.98%).

A total number of 573 (26.5%) patients reported awakenings during the night due to COPD symptoms and 415 (19.2%) patients have used rescue medication during the night before study visit due to respiratory symptoms, with a mean number (±SD) of puffs of 0.42 (±1.09). In the morning of study visit, a total of 673 (31.1%) patients have reported the use of rescue medication due to COPD symptoms with a mean number (±SD) of puffs of 0.58 (±1.02). More than half of the patients (58.6%) reported activity limitations due to early morning symptoms.

Irrespective of the severity of the airflow obstruction, >90 % patients in each severity category experienced COPD symptoms throughout the 24-hour day. The prevalence of COPD symptoms was the highest during the day (>89% of patients, irrespective of the COPD severity). The severity scores of symptoms in each part of the 24-hour increased significantly with airflow obstruction (P<0.001 for all).

The groups of patients presenting night-time and early morning severe symptoms had a significantly higher rate of exacerbations as compared to the group of patients without severe symptoms (P<0.001 for all).

Physical activity patterns

The physical activity assessed by Investigators per their clinical judgement indicated that 47.5% of patients are active (≥ 150 minutes/week of moderate to vigorous exercise, like brisk walk), 42.4% insufficiently active patients (1 – 149 minutes/week of moderate to vigorous exercise, like brisk walk) and 11.9% incompletely active (0 minutes/week of moderate to vigorous exercise, like brisk walk). The analysis of the patient-reported data collected through EVS (exercise as vital signs) questions indicated a different distribution of the same categories (32% active, 35.1 insufficiently active and 32.9% completely inactive). The analysis of concordance between these two assessments of the physical activity level indicated a moderate agreement between patients and Investigators evaluations.

Overall, the mean total time (±SD) spent by patients doing any activity was 21.0 (18.1) hours/week. The mean (±SD) energy expenditure during activity was 4690 (4240.2) Kcal/week. The mean summary index (±SD) of the physical activity was 42.85 (25.94). When using the cut-point score of 51 in the summary index of the YPAS questionnaire, 68.4% of patients classified as sedentary (<30 min/day of moderate activity).

Patients presenting with specific symptoms or cluster of symptoms (e.g., dyspnea during 24-hour day, cough & sputum during 24-hour day and night-time wheezing & dyspnea) had significant lower activity scores as assessed with EVS and YPAS as compared with patients without that symptom or cluster of symptoms.

Correlations

The symptoms during each part of the 24-hour day have significantly inter-related for each potential symptom combination (P<0.001 for all).

The symptoms during each part of the 24-hour day and physical activity evaluated through the interview-administered questionnaires (EVS & YPAS total score) had significant, although weak associations (P<0.001 for all).

The severity of symptoms in any part of the 24-hour day and HrQOL as evaluated with CAT score had a significant correlation (P<0.001).

The severity of daytime and early morning symptoms and FEV1 had a weak correlation.

The physical activity level as assessed with EVS indicated the existence of significant, weak associations with CAT and mMRC (P<0.001).

Conclusion:

Despite regular treatment, the majority of stable outpatients with COPD is still presenting mild to moderate symptoms. Daytime and early morning symptoms were most common, while among individual symptoms cough and dyspnea were most frequently reported. The presence of symptoms impacts and limits the physical activity of patients. While the physical activity level was reduced in this COPD cohort, it seemed to be overestimated by physicians. This suggests that in routine clinical practice there are no standardized approaches of identifying sedentary patients. Additional guidance and easy-to-use tools to allow clinicians to recognize sedentarism among COPD patients and evaluate the improvement of physical activity are needed.