OBSERVATIONAL STUDY REPORT SYNOPSIS

A Study to Evaluate the Symptoms over 24 hours in Patients with Chronic Obstructive Pulmonary Disease - LASSYC Study

An observational, cross-sectional study of primary data collection to describe symptoms over 24 hours and their relationship with adherence to respiratory treatment, direct costs and PRO in stable COPD patients in Brazil.

Milestones:

Milestones	Date
Final Protocol	12-Jun-2017
Study Start Up: contracts in place, regulatory submissions, initiation visits	23-Oct-2017
Inclusion of First Study Subject (FSI)	01-Nov-2017
Inclusion of Last Study Subject (LSI)	29-Jun-2018
Database Lock & Data Extraction	23-Aug-2018
Development of Analytic Datasets	27-Nov-2018
Final Report	26-June-2019

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 Centers:

The study was performed in eight research centers distributed in the Brazil´s Southeastern and Southern regions.

Background/Rationale:

No previous study has evaluated the frequency and severity of Chronic Obstructive Pulmonary

Disease (COPD) symptoms over a period of 24 hours (early morning, daytime and nigth-time symptoms) in stable COPD patients seen in clinical practice in Brazil. COPD is a common disease seen by primary care physicians and one of the most common diseases referred and diagnosed by pulmonologists. According to previous studies, symptoms of COPD can have a substantial impact on patients' quality of life and present a considerable degree of variation for the same degree of airflow limitation.

The objective of this study is to learn more about the burden of symptoms in the real-world population of COPD patients in Brazil. With the real life data coming from this study, it is possible to describe 24-hour COPD symptoms in Brazil and their impact on patients' quality of life and other PROs, the relationship with patients´ behavior regarding adherence to respiratory medication and burden of COPD symptoms in terms of the impact on health economics.

In this sense, in the present study, we assessed and characterized COPD symptoms over a period of 24 hours, by collecting information about the respiratory symptoms experienced at different times of the day and night in patients with stable COPD under real clinical practice conditions. In addition, we evaluated the correlation between each of these symptoms and the GOLD classification, adherence to respiratory treatment, level of dyspnea, disease severity, comorbidities and physical activity. Finally, we will assess the relationship between 24h symptoms and direct cost related to treatment and HRU in the previous year to assess the burden of COPD symptoms.

The present study is based on a similar protocol applied in Latin-American patients, the LASSYC LATAM Study. Extracted data may be used for a Brazilian analysis of these outcomes and may be used in future analyses combined with the results of LASSYC Study for a global view of Latin America.

Objectives:

Primary Objective:

To describe the prevalence, severity and interrelationship of early morning, day and night-time symptoms in patients with stable Chronic Obstructive Pulmonary Disease (COPD) in Brazil.

Secondary Objectives:

1. To evaluate the relationship between early morning, day and night-time symptoms and:
    - Adherence to respiratory treatment;
    - Disease GOLD 2013 classification, severity (BODEx), level of dyspnea (mMRC), comorbidities (COTE);
    - Exacerbation history in previous 12 months;
    - PRO: HRQoL(CAT) and physical activity (IPAQ);
    - Direct Cost of the disease (Healthcare Resource Use (HRU) - in past 12 months and medication costs in last 2 months without any change).

2. To describe treatment of COPD patients in Brazil according therapeutic class and modality (rescue vs maintenance).

No formal hypotheses testing will be performed.

Methods:

Study design:

The Brazilian Study of 24-hour Symptoms in Patients with Chronic Obstructive Pulmonary Disease (LASSYC-BR) was an observational, multicenter, cross-sectional data, non-interventional study. The study was performed between November, 2017 and June, 2018, in eight study sites distributed in the Brazil´s Southeastern and Southern regions.

Data Source(s):

Site staff retrospectively collected the required information from patient's medical records and/or during the single study visit.

At study visit, the investigators collected, for each of the patients, the following data from medical records or clinical interview: social demographics, health insurance system, lifestyle, smoking history, comorbidities, level of dyspnea, disease severity, treatments prescribed for COPD (therapeutic class), inhalation device (pMDI or DPI), modality (rescue/maintenance) and posology within the last 2 months, exacerbations history and healthcare resources utilization during last 12 months. In addition, each patient was asked to provide information about symptomatology related to the disease evaluated during twenty-four hours of the day (daytime), early in the morning (morning) and at night-time, along with adherence to inhalers, health-related quality of life (HRQoL) and level of physical activity.

The dyspnea level was measured by the modified dyspnea scale from the *Medical Research Council* (mMRC). The severity level of COPD was quantified by the BODEx index. Comorbidities were evaluated by the COTE score (COPD specific comorbidity test). The COPD Assessment Test (CAT) was used to define the impact of the disease on health status. Adherence to respiratory medications was performed using the eight-item Morisky Medication Adherence Scale (MMAS-8). Physical activity level was evaluated by the International Physical Activity Questionnaire (IPAQ).

Daytime symptoms, or symptoms occurring on the day prior to the study visit, were evaluated by the Evaluating Respiratory Symptoms (E-RS™) - COPD 2016 questionnaire (previously known as EXACT-RS). The E-RS™ evaluates symptoms occurring on the day prior to the study visit, from the beginning of regular daily activities until the time the patient lied down to sleep. Morning symptoms were analyzed by the Early Morning Symptoms of COPD Instrument (EMSCI). Night-time symptoms were measured by the Night-time Symptoms of COPD Instrument (NiSCI).

The intensity of daytime symptoms was classified as mild, moderate, or severe, according to the distribution of E-RS^{TM} scores in tertiles. The presence of morning symptoms was considered significant, according to two definitions: 1) At least moderate dyspnea associated with any other moderate, severe, or very severe symptom; or 2) At least two of the symptoms evaluated as at least moderate, or a symptom perceived as at least severe. For the analysis of night-time symptoms, two definitions were considered: 1) Any night-time awakening; or 2) If there was presence of at least two of the symptoms evaluated as at least moderate, or a symptom perceived as at least severe.

No additional mandatory intervention, other than that routinely performed at physician visits,

examinations or treatment was requested.

Study Population:

Patients enrolled in the study had stable COPD according to 2013 GOLD criteria. A total number of 602 patients from eight study sites were enrolled, and 593 patients were included in the final study analysis. All patients met all inclusion criteria and none of the exclusion criteria mentioned below:

Inclusion criteria:

1. Male or female patients aged 40 years or older;
2. Patient diagnosed with COPD for 1 year or more;
3. Patient presenting at least one spirometry with COPD criteria, FEV_1/FVC fixed ratio <0.70 post BD, in previous 12 months;
4. Patient is a current smoker or an ex-smoker with a smoking history of ≥ 10 pack-years;
5. Stable patients, as stated in medical records or patient reports during visit, defined as: without treatment due to exacerbation at study visit or within the previous 2 months, and without changes in maintenance COPD treatment regimen over the preceding 2 months (avoid first-time patient from participating in the study);
6. Patients must be able and willing to read and understand written instructions, and understand and complete the questionnaires required by the protocol;
7. After receiving full explanation, patients must have signed an informed consent document indicating that they understand the purpose of and the procedures required for the study and are willing to participate in the study.

Exclusion criteria:

1. Patient with a diagnosis of sleep apnea syndrome or other chronic respiratory disease different from chronic obstructive diseases;
2. An acute or chronic condition that, in the investigator's opinion, would limit the patient's ability to complete questionnaires or participate in this study.

Statistical Methods:

The study was not designed to confirm (or disprove) pre-defined hypotheses. Statistical analyzes were exploratory and descriptive in nature. The descriptive analysis was performed with frequencies and respective 95% confidence intervals for categorical variables, mean and standard deviation for numerical variables with normal distribution, and median and interquartile for numerical variables with non-normal distribution. Pearson's chi-square test and the Student's T test (for dichotomic exposure) were used to compare the different groups, as well as the analysis of variance (ANOVA, three or more categories in the exposure variables) for the outcomes categorical and numerical, respectively.

Patients with different severity of symptoms were compared according to age, sex, body mass index, smoking, physical activity, presence of asthma, COTE index, dyspnea scale, lung function, CAT score, BODEx index, and outpatient and hospital exacerbations. The Pearson correlation test was used to determine the association between the E-RS™ score and the CAT score, lung function, and morning and evening symptom scores. For the association between

symptom prevalence and severity in COPD patients, linear regression for continuous variables, logistic regression for dichotomous variables, Poisson regression for counting variables or ordinal logistic regression for ordinal outcomes was performed. Gross and adjusted analyzes for possible confounding factors with the respective 95% confidence intervals were performed to obtain the measure of effect. For a better understanding of the interrelationships of variables, a hierarchical model of analysis was used, with variables with P values below 0.25 entered the model and were maintained in the adjusted analysis. P values below 0.10 were considered statistically significant.

To evaluate the association between adherence to respiratory treatment and respiratory symptoms (as a continuous score), Poisson regression was used. For the description of the treatment in patients with COPD in Brazil, according to the therapeutic class and modality (rescue versus maintenance), the absolute and relative frequencies were used for the categorical variables and mean and standard deviation for the numerical variables. For the test of differences between variables according to the type of medication, the Student's T Test was applied for the continuous variables. The prevalence of drug use in their respective categories was evaluated.

The cost description is a secondary objective of Lassyc-BR study and will be further subject for analysis and publication. The manuscript and primary statistical analysis were idealized with focus on the primary purpose of the project.

Results:

Demographics and Clinical Characteristics of Patients with COPD

A total of 593 patients were included with mean (±SD) age of 67.7 years (±9.0), being 52.1% male; BMI of 26.4 (±5.3); 15.5% of active smokers, with mean packets / year smoked of 51.2 (±32.9); 39.3% with low level of physical activity; 17.2% with diagnosis of asthma; COTE index of 1.3 (±2.3); dyspnea on the mMRC scale of 2.1 (±1.1); CAT score of 16.9 (±8.5); BODEx index of 2.9 (±1.8); outpatient and hospital exacerbations of 0.9 (±2.4) and 0.2 (±0.5), respectively; with total diurnal symptoms score (E-RS^{TM}) of 8.9 (±7.4); predominance of the dyspnea with RS-dyspnea score of 6.4 (±6.0), with the severity score at the beginning of the morning being 3.0 (±3.8) and at the evening symptom of 2.9 (±4.0).

Characteristics of Patients According to Daytime Symptoms

There was a balance in the distribution of patients regarding mild, moderate, and severe symptoms during twenty-four hours of the day prior to study enrollment. Of the 593 patients, the most symptomatic patients (n=183; 30.8%) showed the lowest level of physical activity ($p=0.002$), highest airflow limitation ($p<0.001$), lowest scores for mMRC, CAT and BODEx (all $p<0.001$) and highest prevalence of outpatient and hospital exacerbations over the last year ($p=0.002$ and 0.043, respectively).

Prevalence and Severity of Symptoms Early in the Morning and at Night-time

The most frequent symptoms were dyspnea, cough, and wheezing. The prevalence of morning and night-time symptoms was similar, except for dyspnea. The distribution was as follows: morning symptoms - dyspnea 45.2%, cough 37.5%, wheezing 24.4%, chest congestion 20.6%, difficulty expelling phlegm 17.5% and chest tightness 15.7%; night-time symptoms - cough 33.3%, dyspnea 33.1%, wheezing 27.0%, chest congestion 19.5%, difficulty expelling phlegm

18.8% and chest tightness 18.3%. Although most of the symptoms have been reported as mild to moderate, approximately 10% of patients have qualified dyspnea as severe or very severe (10.1% early in the morning, 8.5% at night-time).

One hundred and twenty patients (20,2%) reported at least moderate dyspnea associated with any other moderate, severe or very severe symptom early in the morning (definition 1). For night-time symptoms, 107 (18,0%) patients reported at least one night-time awakening due to COPD-associated symptoms. Taking into account definition 2 of at least two of the symptoms evaluated as at least moderate, or one symptom perceived as at least severe, 182 patients (30,7%) had significant symptoms early in the morning and 171 (28,8%) had night-time symptoms.

Characteristics of Patients with Early Morning or Night-time Symptoms

Patients who reported at least moderate dyspnea associated with other moderate, severe or very severe symptom early in the morning (definition 1) were younger, with a higher COTE index, mMRC, CAT, and BODEx and reported a higher number of outpatient exacerbations over the last year (all $p<0.001$). Patients reporting a night-time awakening due to COPD (definition 1) were younger, with a higher mMRC and CAT (all $p<0.001$) and a higher BODEx score ($p=0.001$).

Using the criteria for definition 2, patients with morning symptoms were younger ($p<0.001$), predominantly female ($p=0.022$), with a higher COTE index and mMRC (both $p<0.001$), worse lung function ($p=0.015$ for FEV_1), higher CAT and BODEx (both $p<0.001$), and a higher number of outpatient exacerbations over the last year ($p<0.001$). On the other hand, patients with night-time symptoms were younger ($p=0.039$), predominantly female ($p=0.044$), with a higher COTE index and mMRC (both $p=0.013$ and $p<0.001$, respectively), worse CAT and BODEx scores (both $p<0.001$), and a higher number of outpatient ($p<0.001$) and hospital exacerbations ($p=0.021$) over the last year. Lung function did not differ among patients with or without night-time symptoms.

Severity of Early in the Morning and Night-time Symptoms According to mMRC Dyspnea Scale

It was observed that the higher the dyspnea score, the greater the severity of the morning or night-time symptoms. The CAT score was also described according to the mMRC scale, so that there was a higher score in the higher categories of the dyspnea scale.

Relationship Between Severity of Daytime Symptoms and Presence of Early Morning and Night-time Symptoms

A strong relationship was detected between the presence of early morning and night-time symptoms and the severity of daytime symptoms during twenty-four hours, using definition 1. In 76.1% of patients with early morning symptoms there was a report of severe symptoms during the day, compared with 21.4% of those who had no early morning symptoms. Similarly, 64.7% of patients with night-time symptoms reported severe symptoms during the day, compared with 25.3% of those who had no night-time symptoms. Among those who had early morning and night-time symptoms, about 90% experienced severe symptoms during the day, compared with fewer than 20% of those who had no symptoms early in the morning or at night-time. The same relationship level was detected by the analyses using definition 2.

Characteristics of Patients Classified as Having Asthma or Using Oxygen Therapy

Asthmatic patients were younger (p <0.001), predominantly female (p = 0.001), and had a higher body mass index (p = 0.017). With the exception of these characteristics and the predicted FVC, no other statistical difference was observed. Patients on oxygen therapy smoked less (p <0.001), had more dyspnea (p <0.001), worse lung function and BODEx index (p <0.001), and also more hospital exacerbations (p = 0.016).

Correlations Between Severity of Daytime Symptoms and Presence of Early Morning and Night-time Symptoms, as well as COPD Characteristics

All variables had correlation that was close or >0.6 (moderate to high) by the E-RS^{TM} global score (CAT score: r=0.62, p<0.001; severity score of early morning symptoms: r=0.65, p<0.001; and severity score for night-time symptoms: r=0.60, p<0.001), except for lung function (r=-0.21, p<0.001). In addition, the CAT score had a good relationship with early in the morning and night-time symptom severity. A very high correlation between severity scores for early morning and night-time symptoms (r=0.83; p<0.001) was also seen.

Patients with a concomitant diagnosis of asthma were younger and mostly female with a higher body mass index. Except for these characteristics and predicted FVC, there was no statistical difference in any other parameter.

Overall and Domain Scores of the E-RS^{TM} Questionnaire according to the mMRC Scale

It was observed that, as the mMRC dyspnea scale increases, the overall score and also the E-RS^{TM} scale domains are higher, with the air deficit domain being the most evident. In the cough and phlegm, and chest symptoms this trend is not so obvious, possibly because the maximum amplitude in these scores is low.

Correlation Between Time from the Diagnosis of COPD and the Symptom Severity Score Assessed through the E-RS^{TM} Questionnaire

A very weak negative correlation was observed between the diagnostic time and the severity score of early morning, daytime and night-time symptoms, being around -0.6.

Distribution of Treatments Used by Patients with COPD

The treatments were categorized by therapy class (mono, double or triple therapy) and also by medication. In this sense, were considered LABA, LAMA, ICS isolated or associated, as well as SABA and SAMA associated, and others. Patients who used SABA or SAMA alone or without treatment were not considered. It was observed that more than half of the patients included in the study used triple therapy, and another 23.7% used LABA / ICS.

Adherence to Treatments used by Patients with COPD

Considering a total of 573 persons who responded to all items of the MMAS-8 Scale, the prevalence of high, medium and low adherence was 53.9%, 33.9% and 12.2%, respectively. Patients with low adherence had lower mean age, lower BODEx index, higher CAT score, and better lung function.

Through a linear regression-adjusted analysis for confounding factors between adherence and symptom severity scores in the early morning, daytime and night-time, statistical significance

was observed for low adherence and severity symptom scores at all times of the day studied (early morning symptoms, β=1,68, IC 95% 0,62 – 2,74; daytime symptoms, β=2,12, IC 95% 0,51 – 3,74; and night-time symptoms, β=1,62, IC 95% 0,64 – 2,60).

According to the mMRC scale, in the lowest degree of dyspnea (0 on the mMRC scale) there was about 65% high adherence to drugs, whereas in the highest degree of dyspnea (4 on the mMRC scale) there was 50% adhesion high. It is important to emphasize, however, that the cross-sectional delineation of the study makes it impossible to evaluate the temporality of these findings.

It was also found that the longer the time of diagnosis of COPD, the greater the adherence to drugs, although there was overlap of the confidence intervals.

All categories of adherence presented a greater number of exacerbations that required searching for emergency services than for other places such as outpatient, hospitalization or ICU. Despite the overlap of confidence intervals, those classified as medium adherence had an average of 0.8 (95% CI (0.3 - 1.3) of exacerbations requiring emergency services search against 0.5 (95% CI 0, 4 - 0.6) of those with high adhesion and 0.58 (IC 95% 0.3 - 0.8) of those with low adhesion.

Regarding the adherence according to the different categories of medication, the greatest adhesions were found for LAMA and LABA / LAMA, followed by the LABA / LAMA / ICS combination. The ICS medication had the highest frequency (80%) of medium and low adherence. Adherence to treatment was also evaluated according to the categorization of the drugs in mono, double or triple therapy, leaving categories of LABA / ICS and other drugs, all mutually exclusive. They were not considered patients without treatment and who used only SABA or SAMA in this categorization. Thus, it was seen that the patients in double therapy are the ones that present greater adhesion to the treatment, followed by those in triple therapy. On the other hand, almost 20% of the individuals in monotherapy have low adherence to drug treatment.

Total Exacerbations According to Drug Therapy

In those with triple therapy or use of LABA / ICS, the proportion of three or more exacerbations was approximately 15%, while in those with dual therapy this percentage was 8% and in monotherapy was 4%.

Patients with three or more exacerbations, i.e. outpatient or hospital, used more combinations with LABA/LAMA/ICS, LABA/LAMA, LABA/ICS and ICS. The LAMA /ICS combination was not used for any type of exacerbation. The use of medication for the pattern of outpatient and hospital exacerbations did not differ much. It should be emphasized that due to the cross-sectional design of the study, it is not possible to speak of temporality.

Demographic, Socioeconomic and Clinical Characteristics of the Patients According to the Type of Medication Used

No differences were observed between the demographic and socioeconomic characteristics according to the type of medication used. However, patients who used ICS alone had the highest CAT score and the highest overall score of early-morning, daytime and night-time symptoms (E-RS^{TM}). As these findings are only descriptive, the measures of variability are sometimes superimposed.

Characteristics Related to the Three Different Classification Criteria Proposed By GOLD

According to the GOLD classification of 2007, patients with stage IV had greater adherence to the treatment. In the 2013 classification, individuals classified as "B" tended to adhere less than the other groups. In the classification of 2017, it is difficult to establish any pattern, due to the low sample size distributed in its 16 groups.

When evaluating the E-RS scores (of daytime symptoms) according to the GOLD classification, it was seen that in the 2007 classification there was worsening of the symptoms as the severity increases. The same does not happen in the 2013 and 2017 classifications.

Regarding the type of drug therapy, triple therapy was the most used in stages II to IV of the GOLD classification of 2007, and in categories B, C and D of the classification of 2013. In the classification of 2017, from category ID (exception category II-D) the use of triple therapy was more prevalent.

Conclusion:

Dyspnea was more frequent in the morning period than in the night-time period. Having morning and/or night-time symptoms was associated with the worst symptom severity during twenty-four hours. The intensity of symptoms was strongly associated with worse quality of life and more frequent exacerbations, but weakly associated with airflow limitation.

More than half of the patients included in the study used triple therapy and presented more exacerbations in last year. The most part of patients using triple therapy were classified as stages II to IV of the GOLD 2007, and in categories B, C and D of GOLD 2013.

The greatest adhesions were found in patients using one or two bronchodilators (LAMA or LABA/LAMA), followed by the triple therapy (LABA/LAMA/ICS).