Symptom variability over the course of the day in patients with stable COPD in Brazil: a real-world observational study

Alberto Cukier[1] , Irma de Godoy[2] , Claudia Henrique da Costa[3] ,
Adalberto Sperb Rubin[4] , Marcelo Gervilla Gregorio[5] ,
Aldo Agra de Albuquerque Neto[6] , Marina Andrade Lima[7] ,
Monica Corso Pereira[8] , Suzana Erico Tanni[2] , Rodrigo Abensur Athanazio[1] ,
Elizabeth Jauhar Cardoso Bessa[3] , Fernando Cesar Wehrmeister[9] ,
Cristina Bassi Lourenco[10] , Ana Maria Baptista Menezes[9]

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Disciplina de Pneumologia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.
3. Disciplina de Pneumologia, Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ) Brasil.
4. Universidade Federal de Ciências da Saúde de Porto Alegre, Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS) Brasil.
5. Clínica Médica Netspiro, São Bernardo do Campo (SP) Brasil.
6. Departamento de Pneumologia, Centro de Reabilitação Pulmonar, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.
7. Hospital Dia do Pulmão, Blumenau (SC) Brasil.
8. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.
9. Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Pelotas (RS) Brasil.
10. AstraZeneca do Brasil, São Paulo (SP) Brasil.

Submitted: 24 June 2019.
Accepted: 8 September 2019.

ABSTRACT

Objective: To analyze symptoms at different times of day in patients with COPD. **Methods:** This was a multicenter, cross-sectional observational study conducted at eight centers in Brazil. We evaluated morning, daytime, and nighttime symptoms in patients with stable COPD. **Results:** We included 593 patients under regular treatment, of whom 309 (52.1%) were male and 92 (15.5%) were active smokers. The mean age was 67.7 years, and the mean FEV_1 was 49.4% of the predicted value. In comparison with the patients who had mild or moderate symptoms, the 183 (30.8%) with severe symptoms were less physically active (p = 0.002), had greater airflow limitation (p < 0.001), had more outpatient exacerbations (p = 0.002) and more inpatient exacerbations (p = 0.043), as well as scoring worse on specific instruments. The most common morning and nighttime symptoms were dyspnea (in 45.2% and 33.1%, respectively), cough (in 37.5% and 33.3%, respectively), and wheezing (in 24.4% and 27.0%, respectively). The intensity of daytime symptoms correlated strongly with that of morning symptoms (r = 0.65, p < 0.001) and that of nighttime symptoms (r = 0.60, p < 0.001), as well as with the COPD Assessment Test score (r = 0.62; p < 0.001), although it showed only a weak correlation with FEV_1 (r = −0.205; p < 0.001). **Conclusions:** Dyspnea was more common in the morning than at night. Having morning or nighttime symptoms was associated with greater daytime symptom severity. Symptom intensity was strongly associated with poor quality of life and with the frequency of exacerbations, although it was weakly associated with airflow limitation.

Keywords: Pulmonary disease, chronic obstructive; Signs and symptoms, respiratory; Quality of life; Disease progression; Brazil.

INTRODUCTION

Classically, the management of obstructive diseases has always been based on clinical data.[(1,2)] In the early 21st century, in keeping with the proposal according to which spirometry became mandatory for its diagnosis,[(3)] the main international guidelines adopted a severity classification system of COPD based on the degree of FEV_1 reduction.[(3)] The intention was never to diminish the importance of clinical information; however, in practice, that is what happened. It is interesting to note that the

Brazilian consensus guidelines never ceased drawing attention to clinical symptoms as part of patient care.[(4)]

In recent years, the importance of patient-based outcomes in clinical trials has been emphasized. This trend is reflected in the current global guideline that defines the severity of COPD based on symptoms, pulmonary function, and exacerbations.[(5)] In parallel, the drug arsenal has been greatly increased by the inclusion of several medications, delivered by various inhalation devices, with their own pharmacological characteristics and pharmacodynamics. Finally, the concept of personalized medicine proposes

identifying the pattern of symptoms and the treatment preferences of each patient.

Various articles have assessed the behavior of symptoms in COPD patients around the clock in different populations.[6-17] Most have shown that patient complaints are more common early in the morning. Other studies have drawn attention to nighttime symptoms, such as the one conducted in 2018 by Miravitlles et al.[15] in seven Latin American countries.

Given that patient behavior varies depending on multiple factors, such as cultural, motivational, and climatic factors,[18-20] it is relevant to understand the symptomatic profile of patients in Brazil. In this context, by using the same methodology applied in the study conducted by Miravitlles et al.,[15] the present proposal aims to characterize and determine the prevalence and severity of symptoms early in the morning, during the day, and at nighttime in patients with stable COPD in Brazil, as well as to evaluate the correlation of each symptom with the severity of the disease.

METHODS

The study entitled "A Study to Evaluate Symptoms Over 24 Hours in Patients With Chronic Obstructive Pulmonary Disease - LASSYC Study (LASSYC-BR)", registered with ClinicalTrials.gov (identifier: NCT03381560), was a multicenter, cross-sectional, observational, non-interventional study. The aim of the study was to characterize the prevalence and severity of symptoms from the beginning of regular daytime activities to bedtime (daytime symptoms), in the early morning (morning symptoms), and at nighttime in patients with stable COPD in Brazil. The study was conducted between November of 2017 and June of 2018, at eight research centers, distributed throughout the southeastern and southern regions of Brazil and detailed in the online Supplement (http://www.jornaldepneumologia.com. br/detalhe_anexo.asp?id=71; Figure S1), with the approval of the ethics committees of each institution. All the patients gave written informed consent.

The patients were in outpatient follow-up and were included consecutively. The inclusion and exclusion criteria are detailed in the online Supplement (Methods S1).

The following information, obtained from medical records or from interviews conducted during the study visits, was collected from each patient: demographic data, lifestyle, history of smoking, comorbidities, dyspnea level, COPD severity, and the history of exacerbations in the last 12 months. Patients provided data on daytime, morning, and nighttime disease-related symptoms, as well as on health-related quality of life and level of physical activity.

Dyspnea level was measured using the modified Medical Research Council (mMRC) dyspnea scale.[21] The level of COPD severity was quantified using the **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **Ex**acerbations index (BODEx).[22] Comorbidities were assessed using the COPD-specific **CO**morbidity **TE**st (COTE) score.[23] The COPD Assessment Test (CAT)

was utilized to define the impact of the disease on health status.[24]

Daytime symptoms were assessed using the **EXA**cerbations of **C**OPD **T**ool (EXACT)-Respiratory Symptoms (E-RS) questionnaire, designed for use in clinical trials to assess the effectiveness of therapeutic interventions regarding symptoms.[25,26] The E-RS evaluates symptoms that have occurred on the day prior to a study visit, from the beginning of regular activities until the patient lies down to sleep.[25] The E-RS provides a total score, ranging from 0 to 40, and three subscales: RS-dyspnea (scale 0-17); RS-cough and sputum (scale 0-11); and RS-symptoms in the chest (scale 0-12). Higher scores translate to greater symptom intensity.

Morning symptoms (on the day of a study visit, from the time patients got out of bed to begin their daytime activities until they were ready for routine activities) were analyzed using the Early Morning Symptoms of COPD Instrument.[27]

Nighttime symptoms (from the time the research subject went to bed the night before until rising out of bed to begin daytime activities on the day of a study visit) were measured using the Nighttime Symptoms of COPD Instrument (online Supplement; Methods S1).[28]

The intensity of daytime symptoms was classified as mild, moderate, or severe, according to the distribution of E-RS scores in tertiles. The questionnaire has no predetermined cutoff levels.

In the study conducted by Miravitlles et al.,[15] the presence of morning symptoms was considered significant in cases of moderate, intense, or very intense dyspnea, associated with any other moderate, intense, or very intense symptoms (definition 1). To evaluate the influence of different definition criteria on the prevalence of symptoms, we also adopted a second definition: at least two of the evaluated symptoms classified as being at least moderate or one symptom perceived as being at least intense (definition 2). Similarly, for the analysis of significant nighttime symptoms, two definitions were considered: any nocturnal awakening (definition of the study conducted by Miravitlles et al.)[15]; or at least two symptoms assessed as being at least moderate or one symptom perceived as being at least severe. The level of physical activity was assessed using the International Physical Activity Questionnaire.[29]

Considering the primary outcome of the study (the occurrence of morning, daytime, and nighttime symptoms), we calculated the sample size based on the estimated prevalence of the outcome in each period. A 30-40% prevalence of the outcome was considered, with an estimated error of 5%, a confidence interval of 95%, and the addition of 5% for possible losses. Therefore, the estimated sample size required was 600 patients.

Statistical analysis

Descriptive analyses were performed to show absolute frequencies using the chi-square test for heterogeneity to describe morning, daytime, and nighttime symptoms.

Pearson's correlation test was used in order to obtain the correlation coefficient of FEV_1 symptom scores. All analyses were performed with the Stata statistical package, version 15.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Patients

We included 593 patients whose demographic and clinical characteristics are shown in Table 1. The mean age was 67.7 ± 9.0 years. The mean FEV_1 was 49.4% ± 17.5% of the predicted value. In the sample, 92 patients (15.5%) were active smokers and 102 (17.2%) reported having a concomitant diagnosis of asthma. The complete results of the questionnaires concerning symptoms were available for 565 patients.

Patient characteristics according to daytime symptoms

There was a balance in the distribution of patients regarding mild, moderate, and severe daytime symptoms. Compared with the mild and moderate symptoms groups, the severe respiratory symptoms group had higher proportions of patients with a low level of physical activity (p = 0.002), greater dyspnea severity on the mMRC scale (p < 0.001), greater airflow limitation. (p < 0.001), worse CAT scores, and worse BODEx scores (p < 0.001 for both), as well as a higher prevalence of outpatient and inpatient exacerbations in the last year (p = 0.002 and p = 0.043, respectively; Table 1).

Prevalence and intensity of morning and nighttime symptoms

The most common symptoms were dyspnea, cough, and wheezing (Figure 1). The prevalence of morning and nighttime symptoms was similar, except for dyspnea. In the sample as a whole, the morning symptoms were cough, in 37.5% of the patients; wheezing, in 24.4%; dyspnea, in 45.2%; chest tightness, in 15.7%; chest congestion, in 20.6%; and difficulty expelling phlegm, in 17.5%. The nighttime symptoms were cough, in 33.3% of the patients; wheezing, in 27.0%; dyspnea, in 33.1%; chest tightness, in 18.3%; chest congestion, in 19.5%; and difficulty expelling phlegm, in 18.8%. Although most symptoms were described as mild or moderate, approximately 10% of patients rated their dyspnea as severe or very severe (in the morning, in 10.1%; and at night, in 8.5%).

Of the 593 patients in the sample, 120 (20%) reported moderate, intense, or very intense dyspnea associated with any other moderate, intense, or very intense morning symptom (definition 1). Regarding nighttime symptoms, 107 (18%) patients reported at least one nocturnal awakening due to symptoms associated with COPD.

In relation to definition 2 (at least two of the symptoms assessed as being at least moderate or one perceived as being at least intense), 182 (31%) and 171 (29%) patients had significant morning and nighttime symptoms, respectively.

Characteristics of patients with morning or nighttime symptoms

Patients who reported moderate, intense, or very intense dyspnea associated with any other moderate, intense, or very intense morning symptom (definition 1) were younger, had higher COTE, mMRC, CAT, and BODEx scores, and reported a higher number of outpatient exacerbations in the last year (p < 0.001 for all).

Patients who reported nocturnal awakening due to COPD (definition 1) were younger, had higher mMRC scores, and had higher CAT scores (p < 0.001 for all), as well as having higher BODEx scores (p = 0.001; Table 2).

Using the criteria of definition 2, we observed the following (online supplement; Table S1): patients with morning symptoms were younger (p < 0.001); were predominantly male (p = 0.022); had higher COTE, mMRC, CAT, and BODEx scores (p < 0.001 for all); had worse pulmonary function, as determined by FEV_1 (p = 0.015); and had a higher number of outpatient exacerbations in the past year (p < 0.001).

Patients with nighttime symptoms were younger (p = 0.039); were predominantly female (p = 0.044); had higher COTE and mMRC scores (p = 0.013 and p < 0.001, respectively); had worse CAT and BODEx scores (p < 0.001 for both); had a higher number of outpatient exacerbations in the past year (p < 0.001); and had a higher number of inpatient exacerbations in the past year (p = 0.021). Pulmonary function did not differ between the patients with and without nighttime symptoms.

Association between the intensity of daytime symptoms and the presence of morning and nighttime symptoms

We detected a strong association between the presence of morning and nighttime symptoms and the intensity of daytime symptoms using definition 1. Of the patients with morning symptoms, 76.1% reported severe daytime symptoms, compared with only 21.4% of those without morning symptoms. Similarly, 64.7% of the patients with nighttime symptoms reported severe daytime symptoms, compared with only 25.3% of those without nighttime symptoms. Among those with morning and nighttime symptoms, approximately 90% had severe daytime symptoms, compared with less than 20% of those with no morning or nighttime symptoms (Figure 2). The same level of association was detected by analyses using definition 2 (online Supplement; Figure S2).

Correlations between the intensity of daytime symptoms and the presence of morning and nighttime symptoms, as well as COPD characteristics

The correlation matrix between some COPD characteristics and the overall E-RS score is presented

Table 1. Demographic and clinical characteristics of COPD patients, according to the intensity of daytime symptoms.[a,b]

Characteristic	All patients (n = 593)	Symptom severity			p*			
		Mild (n = 216)	Moderate (n = 166)	Severe (n = 183)	Overall	Mild vs. moderate	Mild vs. severe	Severe vs. moderate
Age, years	67.7 ± 9.0	69.1 ± 9.0	67.3 ± 9.1	66.2 ± 8.4	0.003	0.133	0.003	0.707
Male	309 (52.1)	121 (56.2)	89 (53.6)	81 (44.3)	0.052	0.640	0.019	0.081
BMI, kg/m^2	26.4 ± 5.3	26.3 ± 4.8	26.3 ± 5.5	26.6 ± 5.7	0.781	1.000	1.000	1.000
Active smokers	92 (15.5)	30 (13.9)	31 (18.7)	23 (12.6)	0.243	0.206	0.699	0.115
Smoking history, pack-years	51.2 ± 32.9	50.9 ± 35.3	48.7 ± 28.8	53.8 ± 33.3	0.338	1.000	1.000	0.431
Levels of physical activity					0.002	0.040	0.001	0.172
Low	233 (39.3)	66 (30.6)	62 (37.4)	86 (47.0)				
Moderate	131 (22.1)	44 (20.4)	44 (26.5)	38 (20.8)				
High	229 (38.6)	106 (49.1)	60 (36.1)	59 (32.2)				
Diagnosis of asthma	102 (17.2)	39 (18.1)	27 (16.3)	34 (18.6)	0.839	0.646	0.893	0.570
COTE index	1.3 ± 2.3	1.0 ± 1.9	1.3 ± 2.4	1.6 ± 2.5	0.052	0.694	0.045	0.777
mMRC scale	2.1 ± 1.1	1.5 ± 0.9	2.2 ± 1.1	2.7 ± 0.9	< 0.001	< 0.001	< 0.001	< 0.001
Spirometry								
FVC, % of predicted	70.9 ± 16.4	74.9 ± 16.1	70.0 ± 16.5	67.3 ± 16.3	< 0.001	0.012	< 0.001	0.363
FEV$_1$, % of predicted	49.4 ± 17.5	54.3 ± 16.7	48.0 ± 17.9	44.8 ± 17.2	< 0.001	0.001	< 0.001	0.264
FEV$_1$/FVC	50.9 ± 11.3	53.1 ± 10.7	49.9 ± 11.4	48.7 ± 11.6	< 0.001	0.016	< 0.001	0.937
CAT score	16.8 ± 8.5	10.8 ± 5.9	17.8 ± 7.3	22.7 ± 7.5	< 0.001	< 0.001	< 0.001	< 0.001
BODEx index	2.9 ± 1.8	2.0 ± 1.4	3.1 ± 1.8	3.7 ± 1.7	< 0.001	< 0.001	< 0.001	0.001
Exacerbations								
Outpatient	0.9 ± 2.4	0.6 ± 1.1	0.8 ± 1.2	1.4 ± 3.9	0.002	1.000	0.002	0.044
Inpatient	0.2 ± 0.5	0.1 ± 0.3	0.1 ± 0.4	0.2 ± 0.5	0.043	0.905	0.037	0.526
E-RS score								
Total	8.9 ± 7.3	1.5 ± 1.4	8.9 ± 2.4	17.7 ± 4.1	< 0.001	< 0.001	< 0.001	< 0.001
Breathlessness domain	6.4 ± 6.0	0.6 ± 1.1	6.6 ± 3.9	13.3 ± 3.2	< 0.001	< 0.001	< 0.001	< 0.001
Cough and sputum domain	1.6 ± 1.9	0.7 ± 1.0	1.6 ± 1.9	2.8 ± 2.1	< 0.001	< 0.001	< 0.001	< 0.001
Chest symptoms domain	0.8 ± 1.2	0.2 ± 0.5	0.7 ± 0.9	1.6 ± 1.5	< 0.001	< 0.001	< 0.001	< 0.001
Severity of morning symptoms score	3.0 ± 3.8	0.7 ± 1.4	3.0 ± 2.9	5.7 ± 4.7	< 0.001	< 0.001	< 0.001	< 0.001
Severity of nighttime symptoms score	2.9 ± 4.0	0.7 ± 1.6	2.6 ± 3.5	5.6 ± 4.7	< 0.001	< 0.001	< 0.001	< 0.001
≥ 1 nocturnal awakening due to COPD	107 (18.0)	12 (5.6)	24 (14.5)	66 (36.1)	< 0.001	0.003	< 0.001	< 0.001

BMI: body mass index; COTE: (COPD-specific) **CO**morbidity **TE**st; mMRC: modified Medical Research Council score; CAT: COPD Assessment Test; BODEx: **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **Ex**acerbations; and E-RS: **EXA**cerbations of **C**OPD **T**ool (EXACT)-Respiratory Symptoms. [a]Values expressed in n (%) or mean ± SD. [b]Complete data from 565 patients. Incomplete data from 28 patients. *ANOVA for continuous variables and the chi-square test for categorical variables.
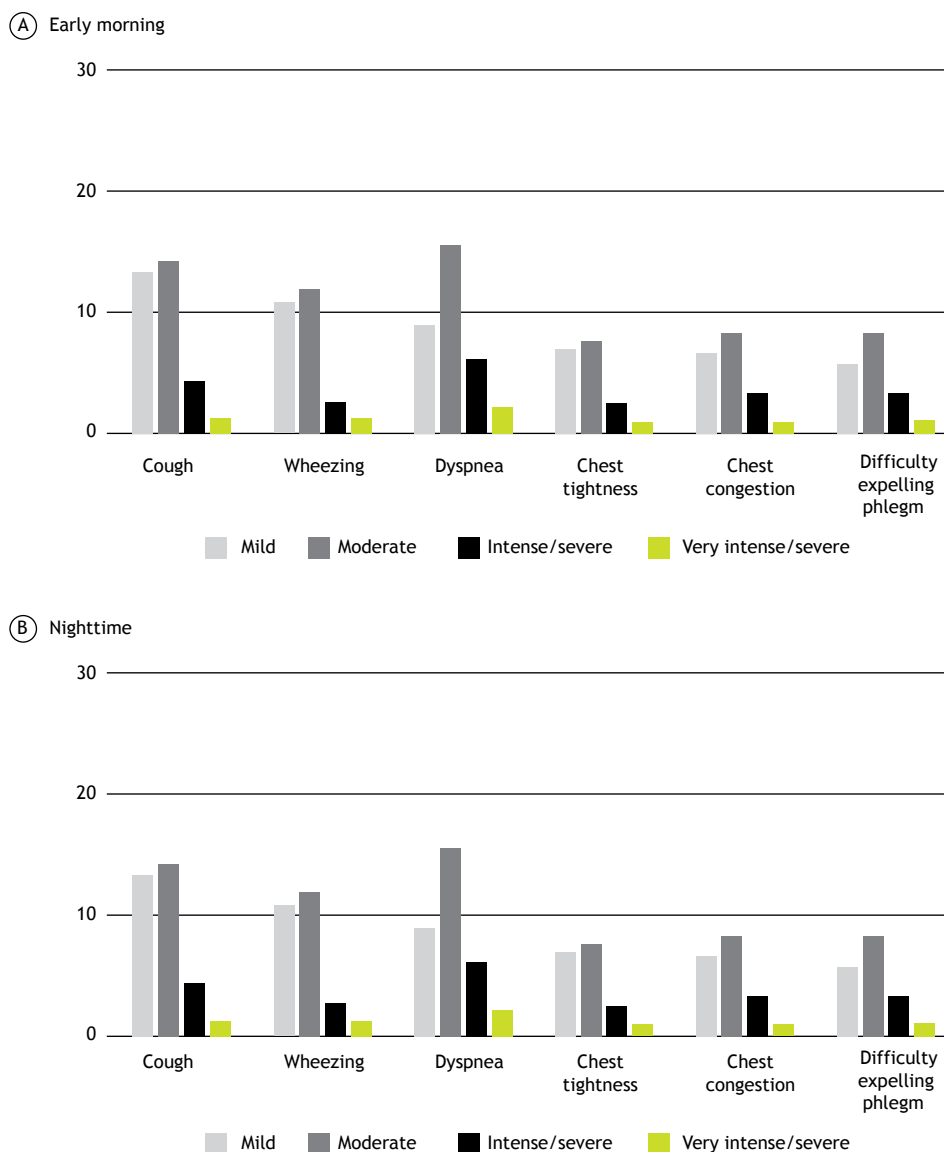
in Table 3. All but one of the variables had a correlation close to or greater than 0.6 (moderate to high), including the global E-RS—CAT score (r = 0.62; p < 0.001), the severity score of morning symptoms (r = 0.65; p < 0.001), and the severity score of nighttime symptoms (r = 0.60; p < 0.001), the exception being pulmonary function (r = −0.21; p < 0.001). In addition, the CAT score correlated well with the severity of morning and nighttime symptoms. We also observed a very strong correlation between morning and nighttime symptom severity scores (r = 0.83; p < 0.001).

Patients with a concomitant diagnosis of asthma were younger, were mostly female, and had a higher body mass index. Except for those characteristics and the

FVC in % of predicted value, there were no statistical differences in any other parameter.

DISCUSSION

We have shown that a considerable proportion of patients with stable COPD remain symptomatic. The strong association between morning and nighttime complaints, as well as the intensity of symptoms during the day, suggest that the symptoms affect the clinical behavior of the disease around the clock. Those results indicate that a focused history-taking investigating this variability may help in defining an individualized therapeutic proposal.

Cukier A, Godoy I, Costa CH, Rubin AS, Gregorio MG, Albuquerque Neto AA, Lima MA,
Pereira MC, Tanni SE, Athanazio RA, Bessa EJC, Wehrmeister FC, Lourenco CB, Menezes AMB

(A) Early morning

(B) Nighttime

Figure 1. Prevalence and intensity of morning symptoms (in A) and nighttime symptoms (in B).

Thirty percent of patients with stable COPD undergoing regular clinical treatment reported severe daytime symptoms. A considerable number reported morning symptoms or nocturnal awakening due to respiratory complaints. Dyspnea was the most common manifestation, being 12% more common in the morning than at night, and 10% of the patients rated their dyspnea as intense or very intense.

Our results were similar to those obtained in the study conducted by Miravitlles et al.,[15] despite the predominance of men in that study (61% vs. 52%) and a higher prevalence of asthma in our population (17.2% vs. 4.5%). Recently, Soler-Cataluña et al.[14] reported that symptoms and their impact on quality of life were less pronounced among patients in Spain than among those in other European countries. The higher proportion of men in the Spanish cohort was

hypothesized to be one of the possible explanations for the difference, because it has been suggested that the impact of COPD would be greater in women.[30] Regarding asthma, its symptomatic behavior in our patients did not differ in relation to the 82.8% of patients who did not have an associated diagnosis of asthma and COPD, suggesting that asthma did not influence the pattern of variability in respiratory complaints.

In recent years, several authors have published studies evaluating the variability of symptoms in patients with stable COPD in different regions.[6-17] Morning symptoms were reported by 37-81% of the patients in the samples, whereas nighttime symptoms were reported by 25-68%. There are several explanations for this disparity, such as the heterogeneity in study design,[31] the method of assessing symptoms, and

Table 2. Demographic and clinical characteristics of COPD patients, according to the presence of morning or nighttime symptoms.[a,b]

Characteristic	Morning symptoms		p*	Nighttime symptoms		p*
	No	Yes		No	Yes	
	(n = 473)	(n = 120)		(n = 486)	(n = 107)	
Age, years	68.3 ± 9.1	65.3 ± 8.3	< 0.001	68.3 ± 8.9	64.9 ± 9.0	< 0.001
Male	255 (53.9)	54 (45.0)	0.081	258 (53.1)	51 (47.7)	0.309
BMI, kg/m^2	26.3 ± 5.1	26.7 ± 5.9	0.475	26.4 ± 5.1	26.4 ± 6.2	0.962
Active smokers	73 (15.4)	19 (15.8)	0.914	74 (15.2)	18 (16.8)	0.680
Smoking history, pack-years	50.3 ± 33.4	54.7 ± 30.4	0.187	51.0 ± 33.4	52.1 ± 30.3	0.761
Levels of physical activity			0.633			0.314
Low	182 (38.5)	51 (42.5)		184 (37.9)	49 (45.8)	
Moderate	104 (22.0)	27 (22.5)		110 (22.6)	21 (19.6)	
High	187 (39.5)	42 (35.0)		192 (39.5)	37 (34.6)	
Diagnosis of asthma	78 (16.5)	24 (20.0)	0.363	86 (17.7)	16 (15.0)	0.496
COTE index	1.1 ± 2.1	1.9 ± 2.7	< 0.001	1.3 ± 2.2	1.4 ± 2.4	0.622
mMRC scale	2.0 ± 1.1	2.6 ± 1.0	< 0.001	2.0 ± 1.1	2.4 ± 1.0	< 0.001
Spirometry						
FVC, % of predicted	71.4 ± 16.1	69.0 ± 17.5	0.163	71.5 ± 16.4	67.9 ± 15.8	0.041
FEV$_1$, % of predicted	50.0 ± 17.3	47.1 ± 18.3	0.109	49.8 ± 17.4	47.3 ± 17.7	0.176
FEV$_1$/FVC	51.1 ± 11.5	49.7 ± 10.5	0.213	50.8 ± 11.4	50.9 ± 11.2	0.937
CAT score	14.8 ± 7.4	24.5 ± 8.0	< 0.001	15.4 ± 7.9	23.4 ± 8.0	< 0.001
BODEx index	2.7 ± 1.7	3.5 ± 1.8	< 0.001	2.8 ± 1.8	3.4 ± 1.8	0.001
Exacerbations						
Outpatient	0.7 ± 1.2	1.7 ± 0.4	< 0.001	0.8 ± 2.5	1.3 ± 1.4	0.028
Inpatient	0.1 ± 0.5	0.2 ± 0.5	0.129	0.1 ± 0.5	0.2 ± 0.6	0.248
E-RS score						
Total	6.8 ± 6.0	17.4 ± 6.1	< 0.001	7.6 ± 6.6	14.8 ± 7.5	< 0.001
Breathlessness domain	5.0 ± 5.5	12.0 ± 4.5	< 0.001	5.7 ± 5.8	9.9 ± 5.6	< 0.001
Cough and sputum domain	1.2 ± 1.6	3.2 ± 2.3	< 0.001	1.3 ± 1.7	3.0 ± 2.3	< 0.001
Chest symptoms domain	0.5 ± 0.8	2.0 ± 1.5	< 0.001	0.6 ± 0.9	1.8 ± 1.5	< 0.001
Severity of morning symptoms score	1.6 ± 2.0	8.7 ± 4.0	< 0.001	2.1 ± 2.8	7.0 ± 5.0	< 0.001
Severity of nighttime symptoms score	1.6 ± 2.5	7.6 ± 5.0	< 0.001	1.9 ± 3.0	7.4 ± 4.6	< 0.001
≥ 1 nocturnal awakening due to COPD	51 (10.8)	56 (46.7)	< 0.001	-	-	-

BMI: body mass index; COTE: (COPD-specific) **CO**morbidity **TE**st; mMRC: modified Medical Research Council score; CAT: COPD Assessment Test; BODEx: **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **Ex**acerbations; and E-RS: **EXA**cerbations of **C**OPD **T**ool (EXACT)-Respiratory Symptoms. [a]Values expressed in n (%) or mean ± SD. [b]Complete data from 565 patients. Incomplete data from 28 patients. *ANOVA for continuous variables and the chi-square test for categorical variables.

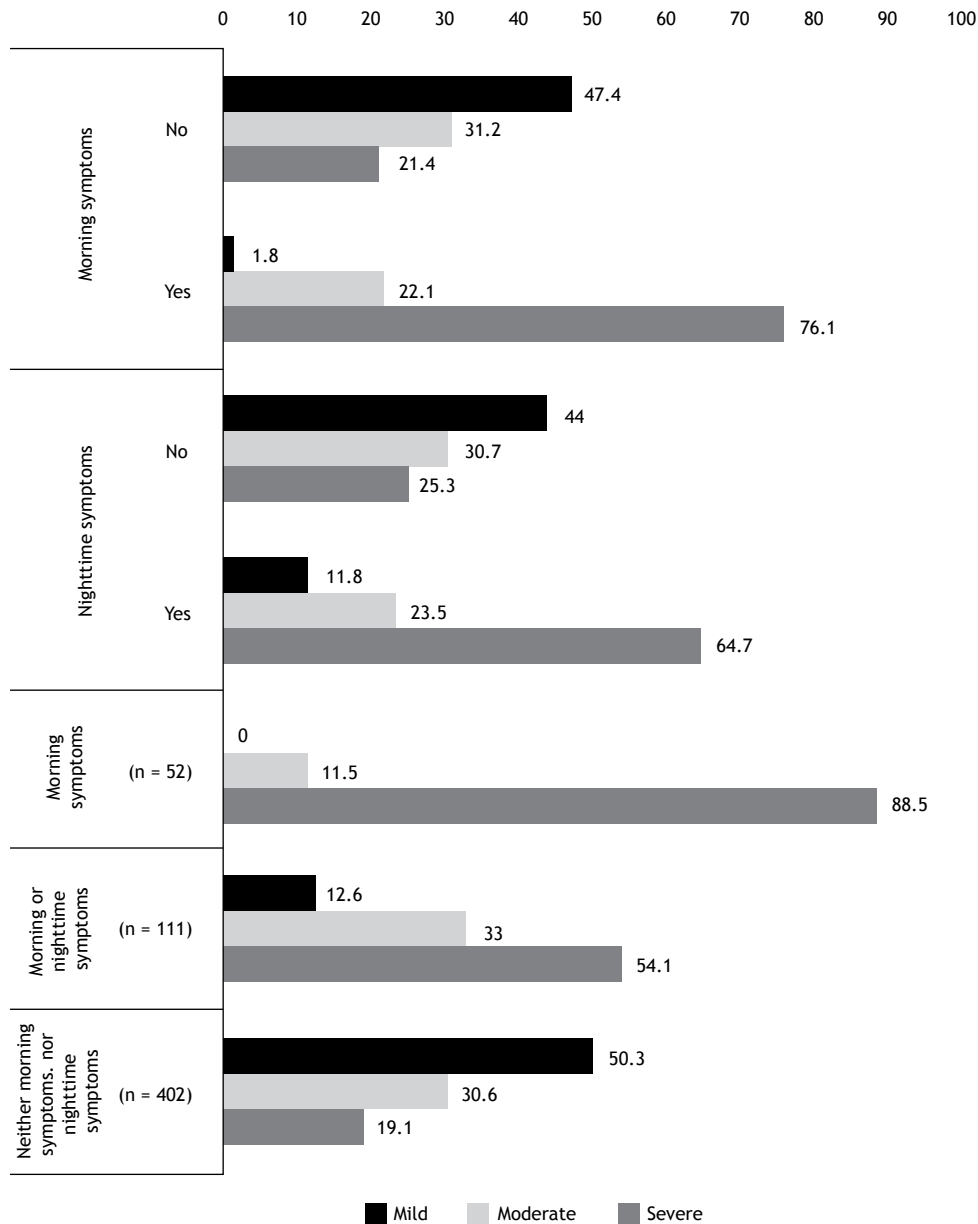behavioral differences between patients in different locations.[18,19,32]

By adopting two forms of grading symptoms, we demonstrated the importance of the assessment method in determining their prevalence. Morning dyspnea was reported by 20% of our patients when the criterion was moderate, intense, or very intense dyspnea accompanied by any other moderate, intense, or very intense symptom. This prevalence increased to 31% by simply changing the criteria to include at least two symptoms assessed as being at least moderate or one perceived as being at least intense. Similarly, the prevalence of nighttime symptoms varied between 18% and 29% due to the change of those two criteria, respectively.

Morning and nighttime symptoms were both found to correlate strongly with the intensity of symptoms around the clock. We also observed a very strong

correlation between morning and nighttime symptom severity scores. However, the correlation between symptoms and the degree of airflow limitation, although statistically significant, was weak. Those data are in line with those of other publications,[6-17] which underscores the importance of assessing the symptomatology of patients and the weak association between the degree of spirometric changes and symptoms.

One of the strengths of our study was that we characterized the symptomatic behavior of COPD patients in Brazil with an adequate sample size. Regarding the methodological aspects, we emphasize that the present study is one of the few in the international literature in which validated questionnaires were used to evaluate morning and nighttime symptoms.[31]

Our study has some limitations. As with all other published studies on the variability of symptoms around the clock, we emphasize that this was a cross-sectional

Cukier A, Godoy I, Costa CH, Rubin AS, Gregorio MG, Albuquerque Neto AA, Lima MA,
Pereira MC, Tanni SE, Athanazio RA, Bessa EJC, Wehrmeister FC, Lourenco CB, Menezes AMB

JBP

Figure 2. Associations between the intensity of daytime and nighttime symptoms and the prevalence of morning and nighttime symptoms.

observational analysis. In addition, as with other studies, we evaluated only the variability of respiratory symptoms without investigating extrapulmonary manifestations. Another limitation is related to the distribution of the participating research centers, all of which treat patients at the secondary and tertiary health care levels and are located in the southeastern or southern regions of the country, thereby limiting the generalizability of the findings. Finally, during the collection of data, there were variations in the availability of medications at most of those centers. Although the patients included in the study had not had any changes in their medication prescriptions for two months, some were not using their usual maintenance treatment regimen.

However, these limitations did not influence the main study outcome, which underscores the importance of evaluating the variability of symptomatology around the clock in our population.

The mechanisms responsible for the temporal variability of respiratory symptoms are unclear. Circadian rhythms probably have an influence. In healthy individuals, it is recognized that FEV_1 is reduced by approximately 150 mL during the night,[33] and a similar reduction has been reported in patients with COPD.[34] It is speculated that these variations contribute to the onset of nighttime and morning symptoms.

Our data have obvious clinical implications. Health professionals are used to questioning COPD patients

Table 3. Correlation matrix between the total score of the global **EXA**cerbations of **C**OPD **T**ool-Respiratory Symptoms instrument, COPD Assessment Test score, FEV_1 in % of predicted, and severity scores of morning and nighttime symptoms.

Parameter	E-RS total		CAT		FEV_1, % of predicted value		Score – morning symptoms	
	r	p	r	p	r	p	r	p
CAT	0.6176	< 0.001						
FEV_1, % of predicted value	−0.2095	< 0.001	−0.1923	< 0.001				
Morning symptoms score	0.6515	< 0.001	0.5857	< 0.001	−0.0428	0.310		
Nighttime symptoms score	0.5982	< 0.001	0.5833	< 0.001	−0.0051	0.904	0.8334	< 0.001

E-RS: **EXA**cerbations of **C**OPD **T**ool (EXACT)-Respiratory Symptoms; and CAT: COPD Assessment Test.

about their symptoms. However, it is not customary to ask patients to report the period of the day during which their complaints prevail, nor is it common to inquire about the impact those complaints have on their activities and well-being. A considerable proportion of patients remain symptomatic despite receiving adequate treatment that follows the treatment guidelines. It is possible that, for some, a personalized approach to treatment that recognizes the particularities of the periods of the day during which the symptoms are at their worst will result in an improvement of symptoms.

When we treat our patients, we use a set of information. Specifically, we evaluate and quantify their symptoms, the frequency and intensity of exacerbations, the behavior of the disease over time, and the impact on activities of daily living.[35] The data presented in this study, combined with those published previously, suggest that inquiring about the variability of symptoms throughout the day and night should be an integral part of a proper history-taking.

AUTHOR CONTRIBUTIONS

All of the authors contributed to the collection and interpretation of the data. AMBM and FCW performed the statistical analysis of the data, and all of the authors were involved in their interpretation. AC wrote the manuscript. All of the authors contributed to the critical revision of the manuscript and have approved the final version for submission to the JBP.

REFERENCES

1. Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions: a report of the conclusions of a CIBA guest symposium. Thorax. 1959;14(4):286-99. https://doi.org/10.1136/thx.14.4.286

2. Johnson MA, Woodcock AA, Rehahn M, Geddes DM. Are "pink puffers" more breathless than "blue bloaters"? Br Med J (Clin Res Ed). 1983;286(6360):179-82. https://doi.org/10.1136/bmj.286.6360.179

3. Pauwels RA, Buist SA, Calverley PMA, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163(5):1256-76. https://doi.org/10.1164/ajrccm.163.5.2101039

4. Sociedade Brasileira de Pneumologia e Tisiologia. II Consenso Brasileiro sobre Doença Pulmonar Obstrutiva Crônica - DPOC - 2004. J Bras Pneumol. 2004;30(Suppl 5):S1-S42.

5. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [homepage on the Internet]. Bethesda: GOLD [cited 2019 Jan 10]. Global Strategy for the Diagnosis, Management, and Prevention of COPD - 2019 Report. [Adobe Acrobat document, 155p.]. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

6. Espinosa de los Monteros MJ, Peña C, Soto Hurtado EJ, Jareño J, Miravitlles M. Variability of respiratory symptoms in severe COPD. Arch Bronconeumol. 2012;48(1):3-7. https://doi.org/10.1016/j.arbres.2011.07.004

7. Kessler R, Partridge MR, Miravitlles M, Cazzola M, Vogelmeier C, Leynaud D, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J. 2011;37(2):264-72. https://doi.org/10.1183/09031936.00051110

8. Kim YJ, Lee BK, Jung CY, Jeon YJ, Hyun DS, Kim KC, et al. Patient's perception of symptoms related to morning activity in chronic obstructive pulmonary disease: The SYMBOL study. Korean J Intern Med. 2012;27(4):426-35. https://doi.org/10.3904/kjim.2012.27.4.426

9. Kuyucu T, Güçlü SZ, Saylan B, Demir C, Senol T, Güner S, et al. A cross-sectional observational study to investigate daily symptom variability, effects of symptom on morning activities and therapeutic expectations of patients and physicians in COPD-SUNRISE study. Tuberk Toraks. 2011;59(4):328-39. https://doi.org/10.5578/tt.3268

10. Miravitlles M, Worth H, Soler Cataluña JJ, Price D, De Benedetto F, Roche N, 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. https://doi.org/10.1186/s12931-014-0122-1

11. Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. Curr Med Res Opin. 2009;25(8):2043-8. https://doi.org/10.1185/03007990903103006

12. Price D, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of night-time symptoms in COPD: a real-world study in five European countries. Int J Chron Obstruct Pulmon Dis. 2013;8:595-603. https://doi.org/10.2147/COPD.S48570

13. Roche N, Small M, Broomfield S, Higgins V, Pollard R. Real world COPD: association of morning symptoms with clinical and patient reported outcomes. COPD. 2013;10(6):679-86. https://doi.org/10.3109/15412555.2013.844784

14. Soler-Cataluña JJ, Sauleda J, Valdés L, Marín P, Agüero R, Pérez M, et al. Prevalence and Perception of 24-Hour Symptom Patterns in Patients With Stable Chronic Obstructive Pulmonary Disease in Spain. Arch Bronconeumol. 2016;52(6):308-15. https://doi.org/10.1016/j.arbres.2015.11.010

15. Miravitlles M, Menezes A, López Varela MV, Casas A, Ugaldee L, Ramirez-Venegas A, et al. Prevalence and impact of respiratory symptoms in a population of patients with COPD in Latin America: The LASSYC observational study. Respir Med. 2018;134:62-69. https://doi.org/10.1016/j.rmed.2017.11.018

16. Stephenson JJ, Cai Q, Mocarski M, Tan H, Doshi JA, Sullivan SD. Impact and factors associated with nighttime and early morning symptoms among patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:577-86. https://doi.org/10.2147/COPD.S76157

17. Tsiligianni I, Metting E, van der Molen T, Chavannes N, Kocks J. Morning and night symptoms in primary care COPD patients: a cross-sectional and longitudinal study. An UNLOCK study from the IPCRG. NPJ Prim Care Respir Med. 2016;26:16040. https://doi.org/10.1038/npjpcrm.2016.40

18. Pitta F, Breyer MK, Hernandes NA, Teixeira D, Sant'Anna TJ, Fontana AD, et al. Comparison of daily physical activity between COPD patients from Central Europe and South America. Respir Med. 2009;103(3):421-6. https://doi.org/10.1016/j.rmed.2008.09.019

19. Furlanetto KC, Demeyer H, Sant'anna T, Hernandes NA, Camillo CA, Pons IS, et al. Physical Activity of Patients with COPD from Regions with Different Climatic Variations. COPD. 2017;14(3):276-283. https://doi.org/10.1080/15412555.2017.1303039

20. Amorim PB, Stelmach R, Carvalho CR, Fernandes FL, Carvalho-Pinto RM, Cukier A. Barriers associated with reduced physical activity in COPD patients. J Bras Pneumol. 2014;40(5):504-12. https://doi.org/10.1590/S1806-37132014000500006

21. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6. https://doi.org/10.1136/thx.54.7.581

22. Soler-Cataluña JJ, Martínez-García MA, Sánchez LS, Tordera MP, Sánchez PR. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. Respir Med. 2009;103(5):692-9. https://doi.org/10.1016/j.rmed.2008.12.005

23. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(2):155-61 https://doi.org/10.1164/rccm.201201-0034OC

24. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54. https://doi.org/10.1183/09031936.00102509

25. Leidy NK, Sexton CC, Jones PW, Notte SM, Monz BU, Nelsen L,

et al. Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. Thorax. 2014;69(5):443-9. https://doi.org/10.1136/thoraxjnl-2013-204428

26. Leidy NK, Murray LT, Monz BU, Nelsen L, Goldman N, Jones PW, et al. Measuring respiratory symptoms of COPD: performance of the EXACT-Respiratory Symptoms Tool (E-RS) in three clinical trials. Respir Res. 2014;15:124. https://doi.org/10.1186/s12931-014-0124-z

27. Hareendran A, Make BJ, Zaiser E, Garcia Gil E. Evaluation of the psychometric properties of the Early Morning Symptoms of COPD Instrument (EMSCI). Int J Chron Obstruct Pulmon Dis. 2018;13:1633-1645. https://doi.org/10.2147/COPD.S152087

28. Mocarski M, Zaiser E, Trundell D, Make BJ, Hareendran A. Evaluation of the psychometric properties of the Nighttime Symptoms of COPD Instrument, Int J Chron Obstruct Pulmon Dis. 2015;10:475-87. https://doi.org/10.2147/COPD.S75776

29. Ainsworth BE, Bassett DR Jr, Strath SJ, Swartz AM, O'Brien WL, Thompson RW, et al. Comparison of three methods for measuring the time spent in physical activity. Med Sci Sports Exerc. 2000;32(9 Suppl):S457-64. https://doi.org/10.1097/00005768-200009001-00004

30. Naberan K, Azpeitia A, Cantoni J, Miravitlles M. Impairment of quality of life in women with chronic obstructive pulmonary disease. Respir Med. 2012;106(3):367-73. https://doi.org/10.1016/j.rmed.2011.09.014

31. Wu M, Wang Z, Li M, Li K. Daily Symptom Variability in Patients With Stable COPD: A Narrative Review. West J Nurs Res. 2018;40(10):1543-1561. https://doi.org/10.1177/0193945917705132

32. Menezes AM, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities: the PLATINO study: a prevalence study. Lancet. 2005;366(9500):1875-81. https://doi.org/10.1016/S0140-6736(05)67632-5

33. Borsboom GJ, van Pelt W, van Houwelingen HC, van Vianen BG, Schouten JP, Quanjer PH. Diurnal variation in lung function in subgroups from two Dutch populations: consequences for longitudinal analysis. Am J Respir Crit Care Med. 1999;159(4 Pt 1):1163-71. https://doi.org/10.1164/ajrccm.159.4.9703106

34. Calverley PM, Lee A, Towse L, van Noord J, Witek TJ, Kelsen S. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Thorax. 2003;58(10):855-60. https://doi.org/10.1136/thorax.58.10.855

35. Ferreira CA, Cukier A. Evaluating COPD from the perspective of the patient. J Bras Pneumol. 2006;32(2):vii-viii. https://doi.org/10.1590/S1806-37132006000200001