



Sleep-onset time variability and sleep characteristics on weekday and weekend nights in patients with COPD

Daniele Caroline Dala Pola¹ , Raquel Pastrello Hirata¹ ,
Lorena Paltanin Schneider¹ , Mariana Pereira Bertoche¹ ,
Karina Couto Furlanetto^{1,2} , Arthur Eumann Mesas^{3,4} , Fabio Pitta¹ 

1. Laboratório de Pesquisa em Fisioterapia Pulmonar – LFIP – Departamento de Fisioterapia, Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.
2. Centro de Pesquisa em Ciências da Saúde, Universidade Pitágoras-Universidade Norte do Paraná – UNOPAR – Londrina (PR) Brasil.
3. Programa de Pós-Graduação em Saúde Coletiva, Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.
4. Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain.

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ABSTRACT

Objective: To evaluate sleep-onset time variability, as well as sleep characteristics on weekday and weekend nights, in individuals with moderate-to-severe COPD. **Methods:** Sleep was objectively assessed by an activity/sleep monitor for seven consecutive nights in individuals with COPD. For analysis, individuals were divided into two groups according to sleep-onset time variability results, characterized by intrasubject standard deviation of sleep-onset time (SOT_V) ≥ 60 min or < 60 min. **Results:** The sample comprised 55 individuals (28 males; mean age = 66 ± 8 years; and median FEV_1 % of predicted = 55 [38-62]). When compared with the $SOT_V < 60$ min group ($n = 24$), the $SOT_V \geq 60$ min group ($n = 31$) presented shorter total sleep time (5.1 ± 1.3 h vs. 6.0 ± 1.3 h; $p = 0.006$), lower sleep efficiency ($73 \pm 12\%$ vs. $65 \pm 13\%$; $p = 0.030$), longer wake time after sleep onset (155 ± 66 min vs. 115 ± 52 min; $p = 0.023$), longer duration of wake bouts (19 [16-28] min vs. 16 [13-22] min; $p = 0.025$), and higher number of steps at night (143 [104-213] vs. 80 [59-135]; $p = 0.002$). In general, sleep characteristics were poor regardless of the day of the week, the only significant difference being that the participants woke up about 30 min later on weekends than on weekdays ($p = 0.013$). **Conclusions:** Sleep-onset time varied over 1 h in a standard week in the majority of individuals with COPD in this sample, and a more irregular sleep onset indicated poor sleep quality both on weekdays and weekends. Sleep hygiene guidance could benefit these individuals if it is integrated with their health care.

Keywords: Pulmonary disease, chronic obstructive; Sleep; Actigraphy.

INTRODUCTION

Sleep constitutes approximately one third of the average lifetime, and good sleep quality is important for both physical and mental health, especially for patients with a chronic disease.⁽¹⁾ Disturbed sleep is common in individuals with COPD,^(2,3) and it is one of the most important complaints after dyspnea and fatigue.⁽⁴⁾ The most common complaints related to sleep include sleep-onset insomnia, nighttime awakenings and unrefreshing sleep.^(5,6) Upon assessment, many individuals with COPD present poor sleep quality, characterized by decreased sleep efficiency, increased sleep-onset latency and fragmentation of the sleep architecture, independently of the severity of airflow limitation.⁽⁷⁾ Despite the high frequency of these sleep disturbances and their possible influence on clinical outcomes, there are limited data in the literature about the objectively assessed characterization of sleep in individuals with COPD.

Previous studies have investigated the relationship of sleep regularity with metabolic abnormalities,⁽⁸⁾

obesity,⁽⁹⁾ and risk of cardiovascular diseases.^(10,11) In children, there is evidence of an association of low sleep regularity (or high variability) with altered plasma levels of insulin, low density lipoprotein, and C-reactive protein.⁽⁸⁾ In adolescents, a high sleep variability is related to increased consumption of fat and carbohydrates, as well as a higher consumption of snacks after dinner, which is directly related to obesity.⁽⁹⁾ Furthermore, in the elderly, high sleep variability was associated with increased risk of cardiovascular diseases⁽¹⁰⁾ and increased prevalence and incidence of metabolic abnormalities.⁽¹¹⁾ There is also evidence linking sleep irregularity with a higher risk of neurological, respiratory, and gastrointestinal problems, as well as pain and depression.⁽¹²⁾

Sleep irregularity can be measured by sleep-onset time variability (i.e., intrasubject standard deviation of sleep-onset time). Despite the growing interest in this topic in different populations, to the best of our knowledge, there are no studies available describing and exploring the variability of sleep-onset time in individuals

Correspondence to:

Fabio Pitta, Departamento de Fisioterapia – CCS, Hospital Universitário de Londrina, Avenida Robert Koch, 60, Vila Operária, CEP 86038-350, Londrina, PR, Brasil.

Tel.: 55 43 3371-2477. E-mail: fabiopitta@uel.br

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with COPD. Furthermore, only one study investigated differences in sleep characteristics between weekdays and weekends,⁽¹³⁾ a more in-depth approach being required. Therefore, the aims of this study were to analyze the repercussion of sleep-onset time variability on the quantity and quality of sleep in individuals with moderate-to-severe COPD and to describe sleep characteristics on weekday and weekend nights in this population.

METHODS

This was a cross-sectional analysis of retrospective data from a convenience sample of patients evaluated in the Laboratory of Research in Respiratory Physiotherapy at the State University of Londrina, located in the city of Londrina, Brazil. Subjects enrolled in these baseline-only analyses subsequently took part in an unrelated larger longitudinal observational study.⁽¹⁴⁾ The larger study was approved by the local research ethics committee (Protocol no. 123/09), and written informed consent was obtained from all participants.

Inclusion criteria were having a diagnosis of COPD in accordance with the GOLD,⁽¹⁵⁾ no infections or exacerbations in the last three months, and no severe comorbidities interfering with the assessments. The exclusion criterion was not reaching the minimum daily time wearing the activity/sleep monitor, as further described below.

Assessments

Pulmonary function was assessed with a portable spirometer (Spirobank G; MIR, Rome, Italy) in accordance with the American Thoracic Society guidelines⁽¹⁶⁾ and reference values used for the Brazilian population.⁽¹⁷⁾ For characterization, exercise capacity was assessed by the six-minute walk test (6MWT). The test was conducted according to international standardization⁽¹⁸⁾ and reference values for the Brazilian population.⁽¹⁹⁾

Sleep was objectively assessed by the multisensor activity/sleep monitor SenseWear® Pro2 Armband (BodyMedia, Pittsburgh, PA, USA). Individuals were instructed to wear the monitor 24 h a day for seven consecutive days and nights; however, data from daytime physical activity was not analyzed in this study. This device is a small and light multisensor monitor to be worn around the upper region of the right arm (triceps brachii muscle).⁽²⁰⁾ A minimum on-body time of 22 h per day was considered as a valid assessment day, and the sleep monitor should be worn for at least four valid assessment days, Saturday and Sunday included.

The following variables were used to evaluate sleep: total time in bed, total sleep time (TST), sleep efficiency, wake time after sleep onset (WASO), number of sleep bouts, duration of sleep bouts, number of wake bouts, duration of wake bouts, bedtime, wake-up time, and steps at night (Chart 1). The seven-day standard deviation of sleep-onset time was calculated to quantify sleep regularity. The actigraphic signals were scored

as wake or sleep for each one-minute epoch according to increases or decreases in activity count.

We analyzed sleep characteristics as the mean of all valid assessments for each individual, as well as the comparison of these on weekdays and weekends. In addition, individuals were classified into two groups regarding their sleep-onset time variability: those with a higher night-to-night sleep-onset time variability, characterized by an intrasubject standard deviation of sleep-onset time (SOT_v) equal to or higher than 60 min ($SOT_v \geq 60$ min), and those with a lower night-to-night sleep-onset variability ($SOT_v < 60$ min). This cutoff point has already been used in the literature to evaluate the sleep-onset time variability in adults and in the elderly.^(10,11)

Statistical analysis

Analysis of data distribution was performed using the Shapiro-Wilk test. Normally distributed numerical data were described as mean \pm standard deviation and compared using the t-test, whereas non-normally distributed data were described as median [IQR] and compared using the Mann-Whitney test. Categorical variables were compared using the chi-square test. Correlations between sleep variability and clinical outcomes were investigated using Pearson's or Spearman's coefficients according to the normality of the data. Statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA) and the GraphPad Prism software, version 6.0 (GraphPad Software, Inc., San Diego, CA). Statistical significance was set at $p < 0.05$.

RESULTS

The original sample comprised 58 individuals, 3 of whom were excluded because the minimum number of valid days for sleep assessment was not reached. Therefore, the final sample consisted of 55 individuals with moderate-to-severe COPD in accordance with the GOLD definition.⁽¹⁵⁾ The mean number of days and the mean time during which the participants wore the monitor were, respectively, 6.78 ± 0.6 days and 23.3 ± 0.4 h/day. The median sleep-onset time variability in the overall sample was 65 [47-96] min. In general, the sample was characterized by elderly individuals with a mean BMI of 26 ± 5 kg/m² and a relatively preserved exercise capacity (Table 1).

Sleep characteristics

Table 2 shows that, in general, individuals spent a median of approximately 8 h lying in bed for sleep at night, sleep efficiency and TST being approximately 69% and 5.6 h, respectively. When comparing sleep characteristics, patients woke up approximately half an hour later on weekends than on weekdays. There were no statistically significant differences between weekdays and weekends regarding total time in bed, TST, sleep efficiency, WASO, sleep-onset latency, number

Chart 1. Nighttime sleep measurements derived from actigraphic data.

Variable name	Description
Total time in bed (TIB)	Total time spent lying in bed for sleep during the night
Total sleep time (TST)	Sum of all minutes scored as sleep during TIB
Sleep efficiency	TST/TIB, expressed as %
Wake time after sleep onset	Time spent awake during TIB after the first sleep bout
Number of sleep bouts	Absolute number of nocturnal sleep bouts during TIB
Duration of sleep bouts	Mean duration of nocturnal sleep bouts during TIB
Number of wake bouts	Absolute number of nocturnal wake bouts during TIB
Duration of wake bouts	Mean duration of nocturnal wake bouts during TIB
Bedtime	Hour and minute when the individual lies down in bed to sleep at night
Wake-up time	Hour and minute when the individual gets up from bed to start the day
Steps at night	Absolute number of steps eventually taken between bedtime and wake-up time

Table 1. Demographic and clinical characteristics of the participants (N = 55).^a

Variable	Result
Male	28 (51)
Age, years	66 ± 8
BMI, kg/m ²	26 ± 5
6MWD, m	474 ± 76
6MWD, % predicted	88 ± 14
Pulmonary function	
FVC, L	2.2 [1.7-3.0]
FVC, % predicted	76 [60-86]
FEV ₁ , L	1.3 ± 0.5
FEV ₁ , % predicted	55 [38-62]
FEV ₁ /FVC, %	55 [43-63]
GOLD 1/2/3/4, n	1/34/11/9
Comorbidities	
Heart disease, yes/no, %	16/84
Hypertension, yes/no, %	51/49
Diabetes, yes/no, %	22/78

6MWD: six-minute walk distance. ^aValues expressed as n (%), mean ± SD, or median [IQR] according to the normality of data distribution, except where otherwise indicated.

and duration of sleep and wake bouts, bedtime, and steps at night (Table 2).

Sleep-onset time variability

The SOT_v ≥ 60min and the SOT_v < 60min groups comprised 31 individuals (56% of the total sample) and 24 individuals (44% of the total sample), respectively. Table 3 shows that there were no significant differences regarding clinical characteristics, lung function parameters, and comorbidities between the groups. Moreover, Table 4 shows that the SOT_v ≥ 60min group presented worse sleep quantity and sleep quality indicators, such as lower TST, lower sleep efficiency, higher WASO, longer duration of wake bouts, and higher number of steps during the night when compared with the SOT_v < 60min group. Figure 1 illustrates an example of two representative patients, one from each group. Furthermore, there were no significant correlations between sleep variability and the following outcomes: BMI, history of hospitalization, and presence of hypertension or diabetes mellitus.

DISCUSSION

To the best of our knowledge, this is the first study that objectively evaluated sleep characteristics of individuals with COPD comparing weekdays and weekends and that measured sleep-onset time variability. In general, these subjects maintained their sleep patterns throughout the whole week, the only statistically significant difference being the fact that they woke up half an hour later on weekends. Moreover, it was shown that individuals with a higher sleep-onset time variability (i.e., variation of more than 60 min from night-to-night time that they go to bed) presented considerably worse indicators of sleep quantity and quality.

Various methods are available for the investigation of sleep disorders. Polysomnography is a complete diagnostic method that is considered the gold standard for sleep assessment⁽²¹⁾; however, it may be regarded as expensive in certain settings and does not reflect the natural environment of the individuals. Sleep-wake monitoring with accelerometry is a lower-cost method for assessing sleep that is highly correlated with polysomnography⁽²²⁾ and can provide useful information about sleep characteristics in the natural environment. In addition to estimating sleep, accelerometry can also be used as a screening tool for other sleep-related disorders such as insomnia,⁽⁵⁾ restless legs syndrome,⁽²³⁾ and sleep-related hypoxemia.⁽²⁴⁾ Hypoxemia during sleep is very common in individuals with COPD, being reported in up to 70% of patients with daytime saturations between 90% and 95%.⁽²⁵⁾ Supplemental oxygen may improve sleep in individuals with COPD and nocturnal hypoxemia,⁽²⁶⁾ whereas it has been shown that treatment with bronchodilators can also improve sleep quality.⁽²⁷⁾ Actigraphy does not record oximetry during the night, but nocturnal hypoxemia may be associated with a greater number of nocturnal awakenings and lead to sleep fragmentation, and these are easily identified by the instrument.⁽²⁴⁾ In addition to objective records, there is a number of self-reported instruments which investigate the clinical complaints of patients related to sleep, such as the Pittsburgh Sleep Quality Index (PSQI).⁽²⁸⁾ This questionnaire is widely used in clinical practice and has proven to be effective and capable of providing useful information about the quality of sleep. The PSQI has shown worse

Table 2. Sleep characteristics described as the mean per night on weekdays (Monday to Friday; N = 310 nights) and weekends (Saturday and Sunday; N = 113).^a

Variable	Total	Weekdays	Weekends
Total time in bed, h	8 [7-9]	8 [7-9]	8 [7-10]
Total sleep time, h	5.6 [4.3-6.8]	5.7 [4.4-6.9]	5.5 [4.1-6.5]
Sleep efficiency, %	69 [59-81]	70 [60-81]	68 [55-81]
Wake time after sleep onset, min	128 [70-188]	123 [70-176]	136 [74-218]
Sleep-onset latency, min	11 [2-22]	11 [2-23]	10 [2-22]
Number of sleep bouts	7 [5-10]	7 [5-10]	7 [5-9]
Duration of sleep bouts, min	46 [33-71]	47 [33-72]	45 [30-68]
Number of wake bouts	7 [5-9]	7 [5-10]	6 [4-9]
Duration of wake bouts, min	17 [11-25]	16 [11-24]	18 [11-27]
Bedtime, h:min	23:13 [22:07-00:04]	23:17 [22:06-00:06]	23:10 [22:07-00:00]
Wake-up time, h:min	7:15 [6:28-8:06]	7:11 [6:25-8:00]	7:38 [6:39-8:27]*
Steps at night	125 [67-174]	87 [43-174]	112 [48-205]

^aValues are presented as median [IQR]. *p < 0.05 vs. weekdays.

Table 3. Demographic and clinical characteristics of individuals with COPD according to the cutoff point of 60 min for sleep-onset time variability.^a

Variable	Group		p
	SOT _v < 60 min (n = 24)	SOT _v ≥ 60 min (n = 31)	
Male	11 (46)	17 (55)	0.508
Age, years	66 ± 7	68 ± 9	0.206
BMI, kg/m ²	26 ± 5	26 ± 6	0.633
6MWD, m	467 ± 77	479 ± 75	0.542
6MWD, % predicted	88 ± 15	89 ± 12	0.839
Pulmonary function			
FVC, L	2.1 [1.7-3.2]	2.3 [1.8-3.0]	0.993
FVC, % predicted	75 ± 17	71 ± 17	0.472
FEV ₁ , L	1.2 ± 0.4	1.3 ± 0.6	0.437
FEV ₁ , % predicted	49 ± 16	51 ± 18	0.670
FEV ₁ /FVC, %	51 [41-62]	60 [50-64]	0.159
Comorbidities			
Heart disease, yes/no, %	88/12	81/19	0.754
Hypertension, yes/no, %	50/50	52/48	0.906
Diabetes, yes/no, %	21/79	23/77	0.876

SOT_v: sleep-onset time variability; and 6MWD: six-minute walking distance. ^aValues expressed as n (%), mean ± SD, or median [IQR] according to the normality of data distribution, except where otherwise indicated.

quality of sleep in patients with COPD.⁽²⁹⁾ A combined assessment using objective and subjective methods could provide a wider view about sleep disturbances in individuals with COPD. Unfortunately, data from the PSQI were unavailable for the present study.

Individuals with COPD present sleep characteristics that are distinct from the general population. Nunes et al.,⁽³⁰⁾ using accelerometry as a sleep assessment method, showed that individuals with COPD presented worse sleep quality when compared with a control group.⁽³⁰⁾ The present study provides a more detailed characterization of the sleep patterns of individuals with COPD, identifying that sleep quality is severely impaired in this population. In addition, our data showed that the wake-up time on weekends was 30 min later than that on weekdays. Spina et al.⁽¹³⁾ analyzed the sleep of individuals with COPD regarding the severity of the disease, dyspnea, gender, and sleep

on weekends. On weekends, participants had more fragmented sleep and spent more time awake after sleep onset than on weekdays; however, the variable wake-up time was not analyzed.⁽¹³⁾ Although social jet lag (misalignment between social and biological times) takes into consideration the differences in sleep time between weekdays and weekends, we believe that this phenomenon was not present in this study, since our sample was essentially composed of elderly and retired individuals.

In the present study, it can be observed that patients with higher sleep-onset time variability had worse indicators of sleep quality and a higher number of steps at night. The majority of scientific evidence has focused on associations regarding sleep duration or quality,⁽³¹⁾ leaving a gap in the literature regarding other sleep characteristics, such as sleep regularity. A recent systematic review analyzed the associations of

Table 4. Comparison of sleep characteristics of the participants according to the cutoff point of 60 min for sleep-onset time variability.^a

Variable	Group		p
	SOT _v < 60 min (n = 24)	SOT _v ≥ 60 min (n = 31)	
Total time in bed, h	8.2 ± 1.3	8.0 ± 1.4	0.709
Total sleep time, h	6.0 ± 1.3	5.1 ± 1.3	0.006
Sleep efficiency, %	73 ± 12	65 ± 13	0.030
Wake time after sleep onset, min	115 ± 52	155 ± 66	0.023
Sleep-onset latency, min	16 [10-23]	11 [6-19]	0.127
Number of sleep bouts	6.8 [5.8-8.2]	6.9 [5.9-8.9]	0.905
Duration of sleep bouts, min	56 [44-71]	46 [36-64]	0.131
Number of wake bouts	6.6 [5.7-8.1]	6.7 [5.7-8.5]	0.845
Duration of wake bouts, min	16 [13-22]	19 [16-28]	0.025
Bedtime, h:min	23:23 [22:38-23:46]	23:11 [22:02-23:58]	0.553
Wake-up time, h:min	7:20 [6:37-7:55]	7:18 [6:13-8:13]	0.953
Steps at night	80 [59-135]	143 [104-213]	0.002

SOT_v: sleep-onset time variability. ^aValues expressed as mean ± SD or median [IQR] according to the normality of data distribution, except where otherwise indicated.

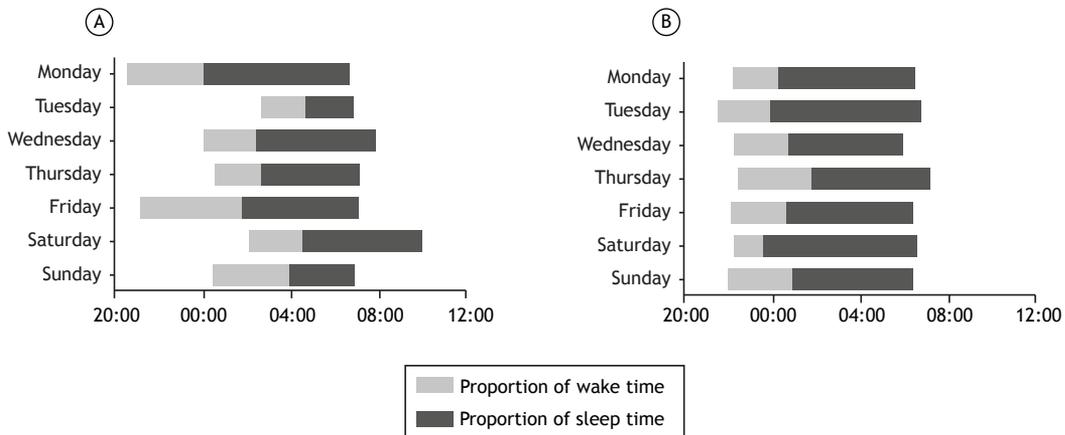


Figure 1. Representation of the sleep patterns over seven days in two individuals with COPD. In A, an individual from the SOT_v ≥ 60 min group (male; 76 years of age; FEV₁ = 57% of predicted; and SOT_v = 131 min). In B, an individual from the SOT_v < 60 min group (male; 75 years of age; FEV₁ = 40% of predicted; and SOT_v = 18 min). Each bar represents the total time in bed for each day of the week; the light gray bar represents the proportion of time spent awake during the total time in bed, and the dark gray bar represents the proportion of time spent sleeping during the total time in bed. Note that in A there is a substantial variation in the sleep-onset time throughout the week, whereas, in B, a regular sleep schedule is maintained. Moreover, the proportion of sleep seems to be lower in A than in B. SOT_v: sleep-onset time variability.

sleep time and sleep regularity with health outcomes, showing that a higher sleep variability was associated with negative health outcomes.⁽³²⁾ Another recent study in the Latin population showed that the regularity of sleep-wake time was as important as sleep duration, since sleep irregularity was associated with a higher prevalence of hypertension and increased systolic blood pressure in adults and in the elderly.⁽³³⁾ Huang & Redline⁽¹¹⁾ showed that for each one-hour increase in sleep-onset time variability, there was an increased odds ratio of 1.23 of prevalent metabolic syndrome when compared with sleep-onset time variability ≤ 30 min (95% CI: 1.96-1.42; p = 0.005) in adults participating in a multi-ethnic study of atherosclerosis. The same group investigated sleep variability in the context of cardiovascular disease and concluded that

irregularities in sleep-onset time and sleep duration may be considered risk factors for cardiovascular disease, regardless of the traditional risk factors and the quantity and/or quality of sleep.⁽¹⁰⁾ There is evidence showing that older people with greater bedtime variability, wake time, and duration of time in bed have higher levels of IL-6 and TNF-α.⁽³⁴⁾ Individuals with COPD also have even higher levels of inflammatory markers than do healthy elderly people.⁽³⁵⁾ It might be that, in individuals with COPD and greater sleep-onset time variability, the inflammatory scenario may be even worse, generating negative consequences on the level of physical activities in daily life,⁽³⁶⁾ sensation of fatigue, and symptoms of depression.⁽³⁷⁾ However, further research is needed to support the hypothesis of a possible relationship between sleep variability and

inflammatory markers in individuals with COPD. It is also known that the association of COPD with other respiratory disorders, such as obstructive sleep apnea, may increase complaints of worsened sleep quality in these patients.⁽³⁾ There seems to be a gap in the scientific literature regarding the possible mechanisms that are involved in or that contribute to the occurrence of sleep variability, whether in COPD alone or in combination with obstructive sleep apnea. This is a broad field of research that can still be explored in the future. The present study, with a cross-sectional and retrospective design, did not aim to establish any causal relationship, but only to characterize sleep variability in individuals with COPD.

Sleep disturbances in individuals with COPD may also be due to non-optimal pharmacological control of the primary disease or due to side effects of pharmacotherapy. The first principle of managing sleep-disordered breathing in COPD should be to optimize the underlying condition, as this may have beneficial effects on breathing.⁽³⁸⁾ Furthermore, despite advances in pharmacological optimization, the role of nonpharmacological therapies remains unquestioned. These include smoking cessation, disease management, use of oxygen therapy, pulmonary rehabilitation, and sleep hygiene measures.⁽³⁹⁾ Since the individuals with COPD with higher sleep-onset time variability presented with characteristics of poor sleep quantity and quality in the present study, these subjects should be strongly encouraged and educated to adopt healthier sleep habits, especially to maintain a regular sleep-onset schedule. Further prospective research is required to evaluate the influence of such interventions on clinical aspects in individuals with COPD.

The present study has some strengths and limitations. Sleep regularity has been shown to be an important aspect associated with worse clinical outcomes in different studies. To our knowledge, this is the first study that evaluated sleep-onset time variability in individuals

with COPD. Another strength of this study is the use of actigraphy, which is a quite useful and accessible method to evaluate sleep-wake characteristics. As for the limitations, patients were not assessed regarding the presence of any sleep disorders, because neither polysomnography nor polygraphy was available for this research project; in addition, the study did not involve a control group. Also, information regarding self-reported clinical complaints related to sleep was unfortunately unavailable. Therefore, these data should be interpreted with caution due to the absence of a control group and subjective complaints about sleep.

In conclusion, the sleep-onset time in the majority of individuals with moderate-to-severe COPD varied in more than one hour in a standard week, and a more irregular sleep onset indicated worse sleep quality. Poor sleep quality in this population occurred both on weekdays and weekends. Sleep hygiene guidance is a simple strategy that could benefit these individuals if it is integrated with their health care.

AUTHOR CONTRIBUTIONS

DCDP: conceptualization, methodology, formal analysis, and drafting of the manuscript. LPS and MPB: methodology, data collection, and data interpretation. KCF: data collection, formal analysis, and critical review of the manuscript. RPH: conceptualization, methodology, formal analysis and interpretation, and drafting of the manuscript. AEM: methodology, formal analysis and critical review of the manuscript. FP: conceptualization, coordination of the project as a whole, formal analysis and interpretation, and drafting and critical review of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

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