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Relevance of Symptom Variability for Control and Management of COPD

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ABSTRACT

Physiological and cellular functions operate in a 24-hour cyclical pattern orchestrated by an endogenous process known as the circadian rhythm. Airway calibre exhibits a circadian variation with maximum values occurring around noon and minimum values in the early morning. The mechanisms behind the daily variation are complex, but it has been speculated that autonomic input to airway tissues via the vagal nerve plays an essential role. In chronic obstructive pulmonary disease (COPD), there is important daily variation of respiratory symptoms, which are present in approximately half of the patients. This time-dependent variability has important consequences since it has an impact on daily life physical activity, sleep quality, severity of symptoms, exacerbations or health-related quality of life, which in turn represents a component of instability within a period previously considered as relatively calm. This article reviews the symptomatic variability in COPD, its pathophysiological basis, characteristics, determinants, potential consequences and therapeutic implications. **(BRN Rev. 2020;6(1):87-101)**

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is mainly characterised by the reduced capacity to generate expiratory flow, which is the result of the complex interaction between peripheral airway obstruction and reduced lung elastic recoil. Traditionally, it has been believed that airflow limitation progresses with time. However, it has recently been discovered that the disease has a high level of heterogeneity with different rates of progression[1]. The commonest respiratory symptoms are chronic cough, sputum production and breathlessness, all of which are generally described as persistent and slowly progressive[2]. Nevertheless, in the course of the disease, patients sometimes experience periods of clinical instability characterised by acute and sustained worsening of these respiratory symptoms, which we usually call exacerbations[3]. These acute events may vary in intensity, duration and/or frequency, but in general, they are associated with adverse consequences such as a worsening of health-related quality of life (HRQoL), reduced physical activity, deterioration of social relationships, disease progression and poor prognosis[4-7]. In the periods between exacerbations, it has always been assumed that respiratory symptoms are unchanged and therefore remain within clinical stability, in contrast to what happens in asthma[8]. However, this traditional paradigm has been challenged over recent years. Several studies have reported that COPD-related symptoms are not perceived uniformly by patients, and that they show not just seasonal variation, but also changes in symptom perception over different weeks or even during a single day[9-18]. This time-dependent variability has important consequences since it has an impact on life activities, sleep quality, severity of symptoms, and exacerbations or HRQoL[10,12,14-19], which in turn represent a component of clinical instability within a period previously considered as relatively calm. This paper reviews in detail the symptomatic variability in COPD, its pathophysiological basis, characteristics, determinants, potential consequences and therapeutic implications.

PATHOPHYSIOLOGY OF SYMPTOMS VARIATION

Physiological and cellular functions operate in a 24-hour cyclical pattern orchestrated by an endogenous process known as the circadian rhythm. Like many other biological variables, airway calibre exhibits a circadian variation during the 24 hours, with maximum values occurring around noon and the minimum values in the early morning[20]. The mechanisms behind the daily variation in symptoms are complex, but it has been speculated that autonomic input to airway tissues via the vagal nerve plays an essential role[21]. Cholinergic tone also follows a normal circadian rhythm, with higher levels during the sleeping hours, which can lead to airflow limitation in patients with COPD and contribute to the variability of symptoms[22]. Changes in pulmonary capacity at night may also reflect changes in both cortisol levels and body temperature[23].

Circadian variation in lung function has been described in patients with stable COPD, including variation in inspiratory capacity (IC)[25], forced expiratory volume in one second (FEV_1)[22,24], forced vital capacity[22,24] and peak inspiratory flow[25]. In addition to altered patterns of lung function, patients with COPD also have

poor sleep quality, increased sleep latency, decreased total sleep time, increased waking after sleep onset, and decreased rapid eye movement and non-rapid eye movement sleep episodes[26,27]. These sleep disturbances may be linked to multiple causes including age, obesity, pharmacotherapy, disease-specific symptoms, including wheezing and cough[28], or the presence of comorbidity sleep disorders (e.g. obstructive sleep apnoea) or other medical conditions. In addition, disrupted sleep in patients with COPD correlates with respiratory symptoms (cough, sputum production, wheezing), nocturnal oxygen desaturation, hypercapnia, and circadian changes in airway calibre and resistance[29].

Patients with COPD frequently experience nocturnal oxygen desaturation episodes[30]. The consequences of nocturnal hypoxaemia (and hypercapnia) may include acute events, arrhythmias and increased pulmonary artery pressure, and long-term sequelae, which include an increased risk of cardiovascular and cerebrovascular diseases[31-33].

Respiratory symptom variability

Daily variability in respiratory symptoms is one of the main characteristics of asthma. This variability has been also associated with lung function changes and poor disease control[34,35]. However, this concept was not widely known until a few years ago in COPD (Table 1). Partridge et al.[9], using an online survey, were among the first authors to show significant daily variation in respiratory symptoms in COPD. The early morning was the worst period of time referred by patients, especially among those with severe disease. Dyspnoea was the most frequent symptom and its perception was associated with a limitation of morning activities. The study also showed the night-time period as a second important period for the perception of symptoms.

Another European survey conducted in 2441 COPD patients reported that over 93% of the patients referred at least one COPD-related symptom (dyspnoea, sputum production, cough, wheezing or thoracic oppression), even while receiving maintenance treatment[10]. Breathlessness was the most frequent symptom (73%), but it was not reported as constant and 63% of the responders perceived variation in one or more symptoms. The variability of symptoms was perceived throughout the year, especially in winter in 60% of the occasions. More than half of the cases also experienced variability during the week and 45% during the same day, with special perception in the early morning. Interestingly, this study also demonstrated the variability of symptoms between different European regions, which was confirmed in the ASSESS study conducted in eight European countries[14]. More than half of the patients included in this latter study had symptoms in all the periods of the day (early morning, daytime and night-time) and almost 80% had symptoms for at least two parts of the 24-h day, despite receiving treatment. The respiratory symptoms were more frequent during the daytime, while cough and sputum production were the most frequent symptoms in the early morning (Fig. 1).

Symptom variability has also shown in another Spanish cohort of 2669 COPD patients using the Nighttime and the Early Morning symptoms of COPD instruments (NiSCI and EMSCI, respectively)[16]. Up to 90% of patients

Table 1. Distribution of symptoms during the day according to different studies

Study (year of publication)	N	Measure method	Early-morning symptoms (%)	Day-time symptoms (%)	Nighttime symptoms (%)	Daily symptom variability (%)
Pardtrige MR et al. (2009)[9]	803	Symptoms questionnaire	37-46%	34-54%	25-34%	NA
Kessler R et al. (2011)[10]	2441	Survey	B: 31.0% S: 56.7% C: 48.9%	B: 66.0% S: 59.1% C: 55.9%	B: 10.6% S: 11.8% C: 17.3%	44.7%
Miravitlles M et al. (2014)[14]	727	Symptoms questionnaire	67.1%	64.4%	52.0%	52.0%
Stephenson JJ et al. (2015)[39]	752	Survey	67.3%	NA	50.0%	NA
Lu M et al. (2017)[17]	1032	Symptoms questionnaire	39.3%	39.5%	21.1%	50.2%
Miravitlles M et al. (2017)[16]	2669	NiSCI/EMSCI	71%	NA	48%	89.6%
Muñoz A et al. (2018)[62]	8185	Survey	53.4%	70.6%	42.0%	NA
Tsiligianni I et al. (2016)[19]	2269	Symptoms questionnaire	51.9%	NA	39.4%	NA

B: Breathlessness; C: Cough; NA: Not available; NiSCI / EMSCI: Nighttime and Early Morning symptoms; S: Sputum.

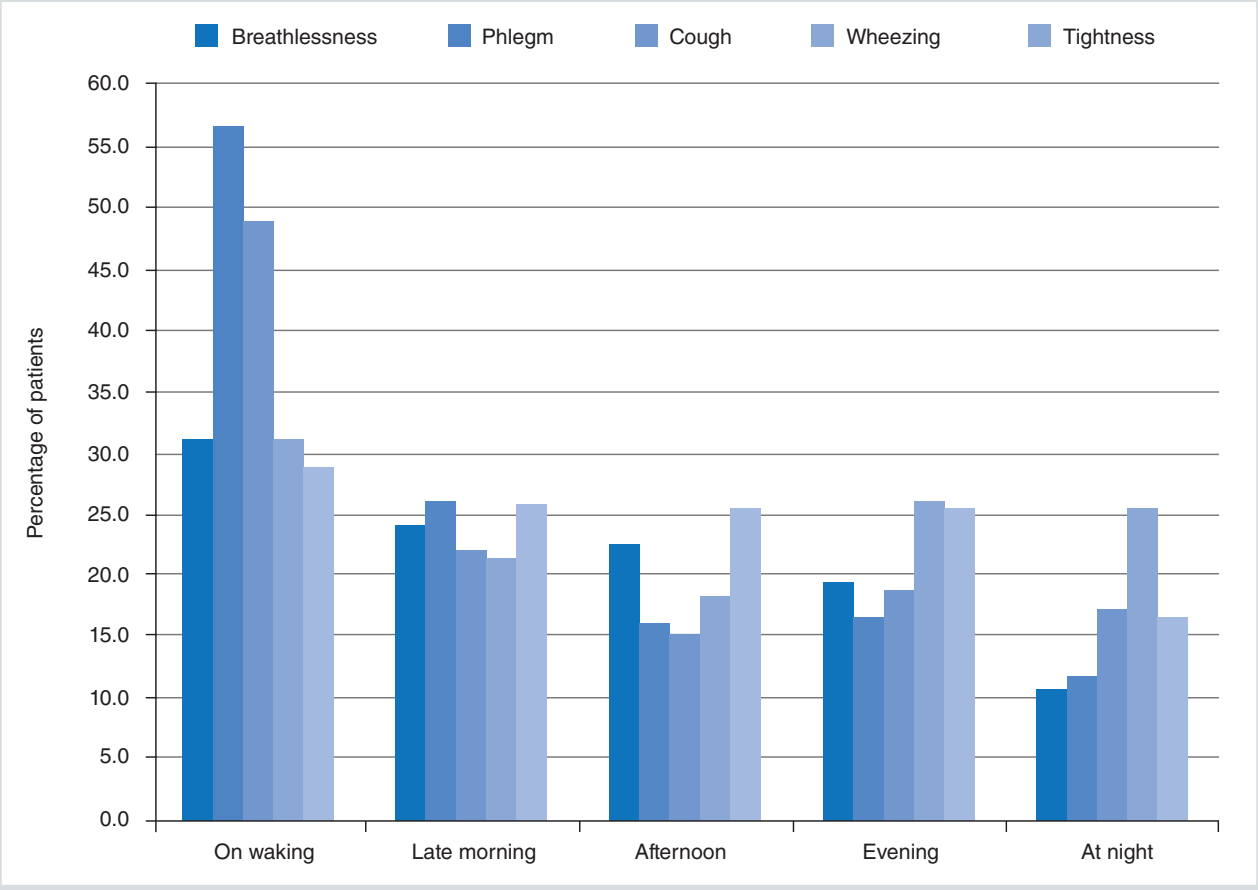

Figure 1. Symptom perception during the day *(reproduced with permission from Lopez-Campos JL et al.[13]).*

showed some type of symptom variability. This variability in "number" (occurrence or disappearance of at least one symptom) was more frequent than the variability in "intensity", which was only observed in 12% of the cases.

One of the least known aspects of symptomatic circadian rhythm is the presence of nocturnal symptoms. However, sleep disturbances and night-time symptoms are frequently experienced by patients with respiratory diseases[36]. Patients with COPD report poorer quality of sleep than those of a similar age without COPD[37]. While epidemiological studies suggest that at least 75% of patients with COPD experience nocturnal symptoms and symptomatic sleep disturbance, physicians are often unaware of these, because they go unreported by patients[38]. In a recent survey, 61% of patients with COPD reported both night-time and early morning symptoms, most frequently coughing, wheezing, and shortness of breath. Of those with night-time symptoms, 78% reported slight-to-extreme sleep disturbances, 34% reported awakening at least once each night and 23% reported difficulty in falling asleep[39]. More than 50% of the patients in the Subpopulations and Intermediate Outcome Measures in the COPD Study (SPIROMICS), a large COPD cohort study, reported poor sleep quality so sleep quality was a significant predictor of the quality of life[40]. In the ASSESS study, 59% of the cases also reported some night-time symptom, mainly cough and sputum production. Poor sleep quality or sleep disturbance in patients with COPD has been shown to be associated with worsened health status, more exacerbations, increased healthcare resource utilisation and increased mortality[14].

METHODS TO ASSESS AND MEASURE SYMPTOM VARIABILITY

A wide variety of methods have been used to record both symptom variability in COPD and the time periods studied. From a temporal point of view, symptom variability has been studied in different seasons of the year, during a weekly period or even on the same day. For the 24-h day analysis, the symptoms are traditionally divided into three parts: early morning, daytime or night-time. Early morning symptoms are defined as those between the time of getting out of bed and 11:00 a.m. Night-time symptoms are those between the time of going to bed and the time of getting up to start the day. The rest of the symptoms are classified as daytime symptoms[14].

To assess variability, the most commonly used approach is to determine the presence or absence of a certain symptom (dyspnoea, cough, sputum production) at a given time in the 24-hour daily cycle. The presence of variability was indirectly suggested by the different distribution of each symptom in one, two or three parts of the day in different proportions. The way to register these symptoms also differs between series. While some studies used telephone or online surveys[9,10], others used specific questionnaires[39,41-45].

The Capacity of Daily Living during the Morning (CDLM) questionnaire, developed by Partridge et al.[41], was the first tool specifically designed to assess the impact of symptoms on the activities during the first hours of the morning. The CDLM questionnaire consists of six questions asking the patient how well he/she can perform six common daily morning activities and evaluating the degree of

difficulty they normally experience. Each item is scored on a scale ranging from 0 (the activity cannot be carried out by the patient) to 5 (the activity is carried out easily). The minimal clinically important difference (MCID) is 0.20.

More recently, the PRO-Morning COPD symptoms questionnaire, which consists of six questions about dyspnoea, cough, sputum production, wheezing, chest tightness, and limitations in the morning, and the severity of these symptoms, rated on a Likert scale from 0 to 10 points (0 for no symptoms and 10 for the worst symptoms)[42], has also been used to assess symptom variability in COPD. A significant difference was observed in the physical activity during the morning and afternoon between patients with severe or few morning symptoms[43].

Other questionnaires, such as the NiSCI and EMSCI, have also been used to assess symptoms[39,44,45]. These questionnaires evaluate three concepts in COPD patients: the occurrence and impact of morning or night symptoms and the use of rescue medication. The scores ranged from 0 (no limitation) to 4 (serious limitations). Using these questionnaires every day for a week, Miravitlles et al.[16] found that 48% of COPD patients described nocturnal symptoms and 71% early morning symptoms. "Number variability" in the early morning or during the night was defined as the appearance or disappearance of one symptom at any time during the 7-day follow-up. "Intensity variability" was defined as changes in at least two levels, of increasing or decreasing intensity, in at least two symptoms during the 7-day period. "Combined variability" was used when both the symptom number and intensity varied. More than 90% of the patients showed number variability. However, only about 12% of the patients reported intensity variability.

Apart from NiSCI, few validated instruments have been used to assess nighttime symptoms. The COPD and Asthma Sleep Impact Scale (CASIS) questionnaire was developed as a self-report measurement to assess the impact of COPD and asthma on sleep quality[40]. This questionnaire was based on patient interviews and is composed of seven items. Although new technology has been developed to monitor coughing during sleep in patients with COPD, more studies are needed to validate the results. Fisher et al.[46], using a LEOSound lung sound monitor, showed that coughing events were found in all the 30 COPD studied, but that most of the coughing periods were non-productive. This correlates with the fact that productive cough is predominantly found in the early morning after getting up from bed[47]. Clearance of airway mucus after sleep may explain the increased frequency of coughing in the first moments after wakening.

DETERMINANTS OF SYMPTOM VARIABILITY

Few studies have assessed the factors associated to the variation in symptoms in COPD. One of the most frequent determinants of variability has been disease severity[10,16,17,39,48]. The more severe the disease, the more the COPD-related symptoms vary. Núñez et al.[48], using CLDM to assess early morning symptoms, have recently shown that lower CLDM scores are related to outcomes of greater COPD severity, in particular with a higher degree of dyspnoea and higher COPD Assessment Test (CAT) and Body mass index,

airflow Obstruction, Dyspnoea, Exacerbations (BODEx) scores. In addition, patients with lower CLDM scores had greater impairment in the lung function test and more frequently required long-term oxygen therapy (LTOT).

Another important factor associated to symptom variability has been the history of exacerbation in the previous year[10,14-16,48]. Patients with the exacerbator phenotype were specifically more prone to show variations in symptoms over a 24-hour day[16,49]. However, exacerbation also has been reported as a consequence of variability. The cross-sectional design of most studies does not allow us to infer the direction of the association. It is conceivable that acute exacerbation might influence symptom variability, because a patient's symptoms would be aggravated before exacerbation and could persist for a while[50] (Fig. 2).

One of the main problems for clinicians is to distinguish COPD exacerbations from symptom variability. Rodriguez-Roisin et al.[51], two decades ago, defined COPD exacerbations as *"a sustained worsening of conditions, from the stable state and beyond day-to-day variations, which is acute in onset and necessitates a change in regular medication in a patient with underlying COPD"*. According to this definition, the difference between the variability of symptoms and exacerbation could be the need for treatment. However, Kessler et al.[10] reported that 39% of patients declared they did not change medication even when the chest symptoms worsened over several days. In contrast, other studies also have shown that, using daily records of symptoms, half of the patients presented "unreported exacerbations" (detected but not reported and therefore not treated)[52]. This type of exacerbations has a similar negative impact on health status as reported exacerbations[52], so there is no way of knowing if they are real COPD exacerbations or if they just indicate a higher symptom variability period. In this context of uncertainty, some authors have suggested that symptom variability without medication change could be a risk factor for COPD exacerbation and poor prognosis, regardless of lung function and previous exacerbation history[18].

The association between clinical phenotypes and variability in symptoms has also been studied recently in an Italian cohort[49]. Regardless of the clinical expression and the treatment used, almost 80% of the patients studied presented early morning and daytime symptoms and just over half of the cases had nocturnal symptoms. The proportion of night-time symptoms was higher in the chronic bronchitis phenotype than in the emphysema or mixed phenotype (54% versus 40% versus 34%, $p = 0.0016$). In another study, the frequent exacerbator phenotype and the asthma-COPD overlap (ACO) phenotype were both associated with greater variability[16]. It was suggested that greater variability in the ACO phenotype was related to the asthmatic component of COPD.

Maintenance treatment with a single long-acting bronchodilator has also been associated with reduced daily symptom variability[10] and more recently, Stephenson et al.[39] have also reported that lower adherence to treatment in the previous year was associated with a higher rate of variability in symptoms.

RELEVANCE OF SYMPTOM VARIABILITY FOR CLINICAL CONTROL

Clinical control in COPD has been defined as a "situation of low clinical impact maintained

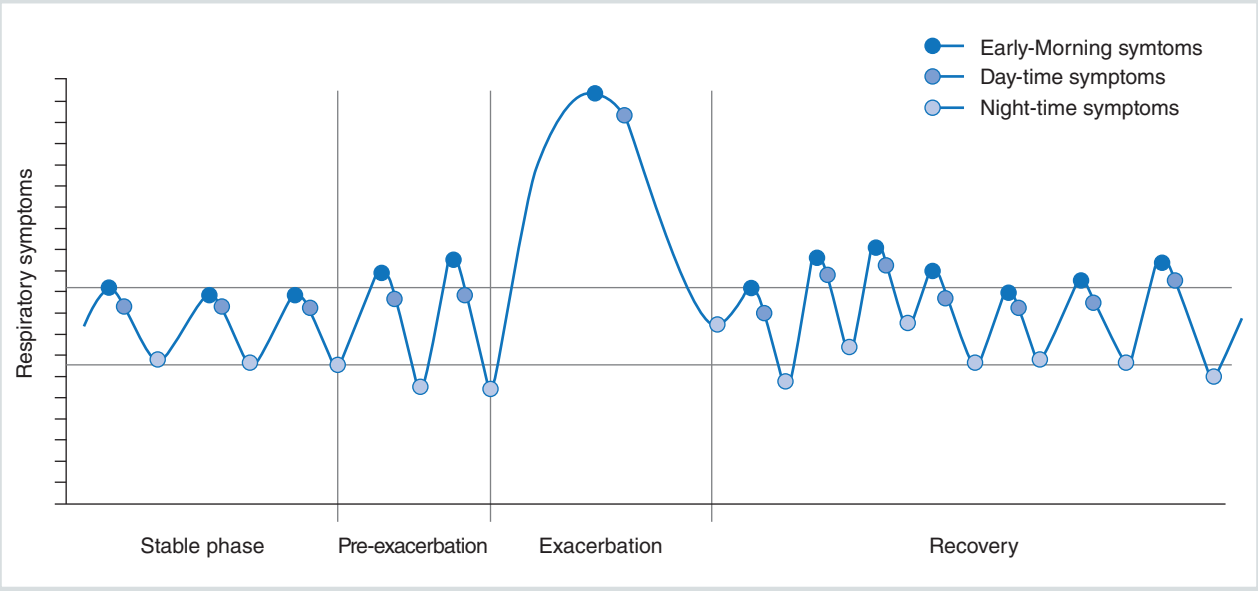

Figure 2. Graphical representation of the respiratory symptom variability.

over time"[53,54]. This definition combines a cross-sectional dimension, "clinical impact", or the impact the disease has on the patient at a given time, which should always be as low as possible (low impact), with a longitudinal dimension, "stability", defined as the absence of exacerbations or clinical worsening over time[55]. A patient who presents a situation of low impact and stability is considered controlled[53]. In order to define the control status, diagnostic criteria have been proposed based on a combination of different clinical parameters (degree of dyspnoea, use of rescue medication, physical activity, sputum colour, presence of exacerbations and the patients' perception of their own health), or an alternative based on the use of validated clinical questionnaires such as the CAT[56] or Clinical COPD Questionnaires (CCQ)[57] (Table 2). These diagnosis criteria have been recently validated, demonstrating that clinical control is an objective which is attainable in the short-term, dynamic over time, sensitive to change and associated with a better outcome in the short and long-term, with a lower risk of future exacerbations and better HRQoL[55,58-60]. For all these reasons, clinical control has been proposed as a new comprehensive therapeutic objective with a key role in clinical decision making[61].

Unfortunately, the impact of symptom variability in clinical control has not yet been studied in COPD. However, several studies have reported that early morning symptoms are associated with severe dyspnoea[16,18,43,62], lower physical activity[43,63], a higher use of rescue medication[39], an increase in the number of exacerbations[12,14] or worse HRQoL[14,39]. Nighttime symptoms have also been associated with an increased risk of exacerbations and worse HRQoL[12,14,67,68]. All these variables make up the concept of control and, for this reason, all

Table 2. Control criteria with adjustment of severity according to the values of FEV_1 % (as percentage of predicted)

Clinical evaluation	
Low clinical impact (must meet at least 3 of the 4 criteria)	
Dyspnoea	0-1 if $FEV_1 \geq 50\%$ 0-2 if $FEV_1 < 49\%$
Rescue medication	≤ 3 times/week
Sputum colour	White
Physical activity	≥ 30 min/day
Clinical stability (must meet both criteria)	
Subjective perception	Same or better
Exacerbations in the last 3 months	None
CAT assessment	
Low impact	
CAT	0-10 if $FEV_1 \geq 50\%$ 0-16 if $FEV_1 < 49\%$
Stability	
Changes in CAT	≤ 2 points
Control	Low impact + Stability

CAT: COPD Assessment Test; FEV_1: forced expiratory volume in one second.

the signs indicate that variability in respiratory symptoms could be adversely associated with clinical control of the disease.

In addition, respiratory symptoms are known to impact physical activity[64]. Exercise limitation occurs even in the early stages of the disease and leads to a poorer prognosis[65]. Morning symptoms are inversely associated with physical activity[43,63]. Recently, van Buul et al.[43], using the PRO-morning COPD symptoms questionnaire, assessed physical activity using an accelerometer for 7 days, 24 hours per day, in a cohort of moderate-severe COPD patients. Patients with a high morning symptoms score spent less time walking, using transport and being at leisure than patients with a lower morning symptom score (Fig. 3).

Morning symptoms are also associated with exacerbation risk and poor HRQoL[14,18,43,62,66]. In the ASSESS study[14], symptoms in any part of the day were also associated with a prior history of exacerbations (all $p < 0.05$) and nighttime and early morning symptoms were associated with the frequency of primary care visits in the year before baseline (both $p < 0.01$). During follow-up, patients with baseline symptoms during any part of the 24-hour day had more exacerbations than patients with no symptoms in each period (all $p < 0.05$); there was also an association between 24-hour symptoms and the frequency of primary care visits (all $p \leq 0.01$). However, although there was a significant association between early morning and daytime symptoms and exacerbations during follow-up (both $p < 0.01$), this significance was not maintained when adjusted for disease severity[66].

In a longitudinal study, Kim et al.[18] found that COPD patients with symptom variability (the variable group) experienced more frequent exacerbations during the follow-up period. Furthermore, this variable setting of patients showed lower lung function, worse dyspnoea symptoms and poorer quality of life. In this study, the symptom variability was assessed during a longitudinal follow-up using the modified Medical Research Council (mMRC) dyspnoea scale (with an arithmetical calculation of the standard deviation in each patient), unlike most series, which use a cross-sectional design. The multivariate analysis showed that the variable group has approximately a two-fold increased risk of annual exacerbator patients. This risk was independent of lung function or previous history of exacerbation. Likewise, frequent exacerbator individuals were associated with death. However, no association was found

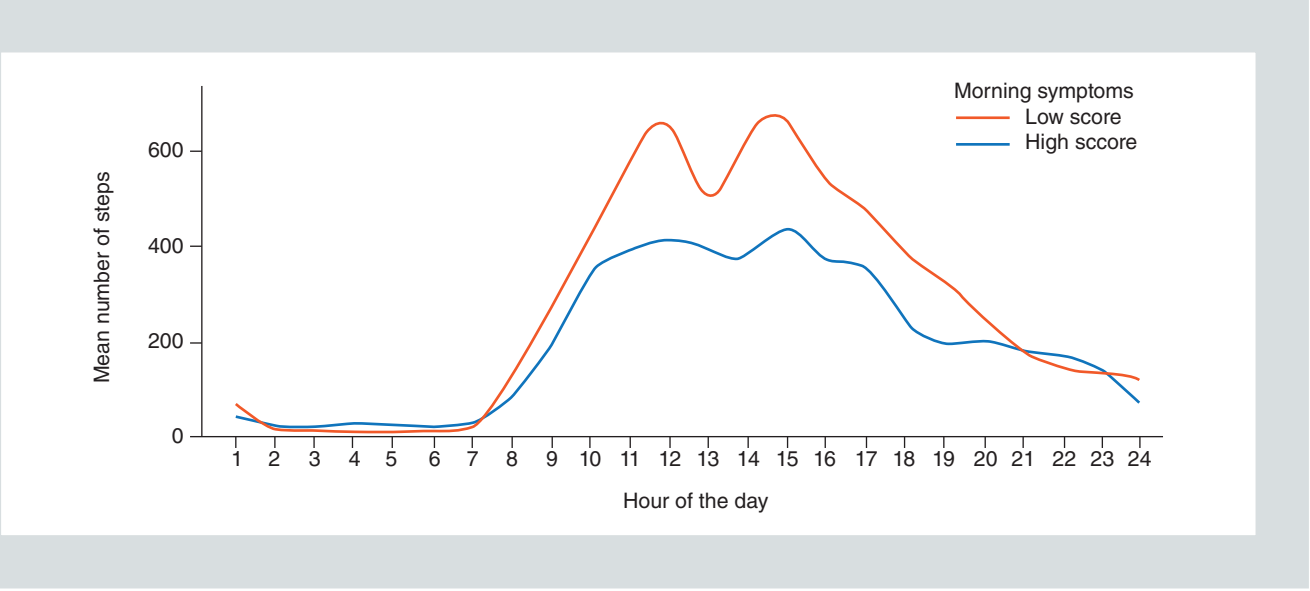

Figure 3. Steps during each hour of the day. Low morning symptom score: score < 17.0; high morning symptom score: score ≥ 17 *(reproduced with permission from van Buul AR et al.[43]).*

between symptom variability and mortality. Instead, they concluded that frequent exacerbator patients had an approximately two-fold higher risk of death. The authors suggested that symptom variability might not be directly associated with mortality but could influence death via increasing risk of exacerbations.

Night-time symptoms, usually less prevalent than those observed at early morning or during daytime, have been associated with an increased risk of cardiac comorbidities and COPD exacerbations[67]. Night-time symptoms reduce sleep quality and may be associated with the long-term effects of sleep deprivation, including cognitive impairment, depression, development or the progression of cardiovascular disease[12,14,38,68]. In the ASSESS study[14,15], up to 60% of the population had nocturnal symptoms. Night-time symptoms were associated with worse HRQoL, as well as with worse scores in both the anxiety and depression subscales of the Hospital Anxiety and Depression Scale (HADS) questionnaire. Price et al.[68] also observed that patients with night-time symptoms had worse HRQoL.

In a real-life study of 8,844 patients with COPD, Muñoz et al.[62] observed that patients with symptoms anywhere in the three parts of the 24-hour cycle suffered a greater impact on their working life. Physical activity also exhibited a similar pattern. These patients also presented higher figures in the CAT score compared to those who did not experience symptoms. Again, the highest score was observed among the cases that showed symptoms in all three parts of the day. The study also revealed worse sleep quality among symptomatic patients.

THERAPY FOR SYMPTOM VARIABILITY

Despite the apparently high prevalence of variability symptoms in patients with COPD, only a few interventional studies have directly targeted

them. In the study by Kessler et al.[9], 51% of the patients declared they did not alter their treatment despite the symptoms worsening during the day, and only 36% reported an increased use of their rescue inhaler. Additionally, 39% of the patients declared they did not change medication even when the chest symptoms worsened over several days.

Likewise, few previous studies have evaluated the impact of treatment on morning symptoms. In a trial comparing the effect of salmeterol/fluticasone versus budesonide/formoterol on lung function, symptoms and activities in the early morning[69], both treatments were revealed equally effective, with budesonide/formoterol showing a more rapid onset of effect, which resulted in greater improvement in the patient's ability to perform morning activities. The Evaluation of efficacy and safety of Symbicort as an add-on treatment to Spiriva in patients with severe COPD (CLIMB) study[70], a 12-week study evaluating the efficacy of adding tiotropium to formoterol/budesonide in 660 subjects with COPD, also found that triple therapy provided rapid and significant improvements in morning symptoms at 5 and 15 minutes compared with tiotropium alone, as measured by the CDLM questionnaire.

Fast long-acting bronchodilators (both long-acting beta-agonists [LABAs] and long-acting muscarinic antagonists [LAMAs]) may play a role to control morning symptoms and to improve HRQoL in patients experiencing an increase of disease-related symptoms in the morning and/or nighttime[13]. The LABAs, such as formoterol, indacaterol, olodaterol and vilanterol act more rapidly than LABAs such as salmeterol, while the LAMAs aclidinium, umeclidinium or glycopyrronium are faster-acting than tiotropium[71].

The effects of bronchodilator over night-time symptoms is another area which has been studied very seldom[22,72,73]. In a 4-week, double-blind study among 36 patients with moderate-to-severe COPD, treatment with ipratropium led to an improvement in oxygen saturation and also in perceived sleep quality[73]. In contrast, in another 4-week, double-blind study among 80 patients with severe stable COPD, evening dosing with tiotropium reduced the daily variation in lung function and improved nocturnal oxygen saturation but did not offer any improvement in perceived sleep quality[72]. Calverley et al.[22] showed that administering the LAMA tiotropium in the evening, rather than in the morning, does not substantially improve lung function parameters during the night.

Several studies have shown that LAMA/LABA combinations lead to greater improvements in FEV_1, higher morning pre-trough and peak inspiratory capacity, greater improvements in dyspnoea symptoms, improved HRQoL and lower use of rescue medication than monotherapy with either of the component agents, with similar adverse events and the cardiac safety profile[74-77]. Of particular interest in the light of symptom variability in COPD, an aclidinium/formoterol combination has been shown to improve overall early morning and nighttime symptom severity and limitation of early morning activities[78] (Fig. 4). The effects of this LAMA/LABA combination over nighttime symptoms were assessed as a secondary variable so further specific studies are needed.

As far as we know, no studies to date have analysed the role of triple therapy on symptomatic variability in COPD. However, indirect

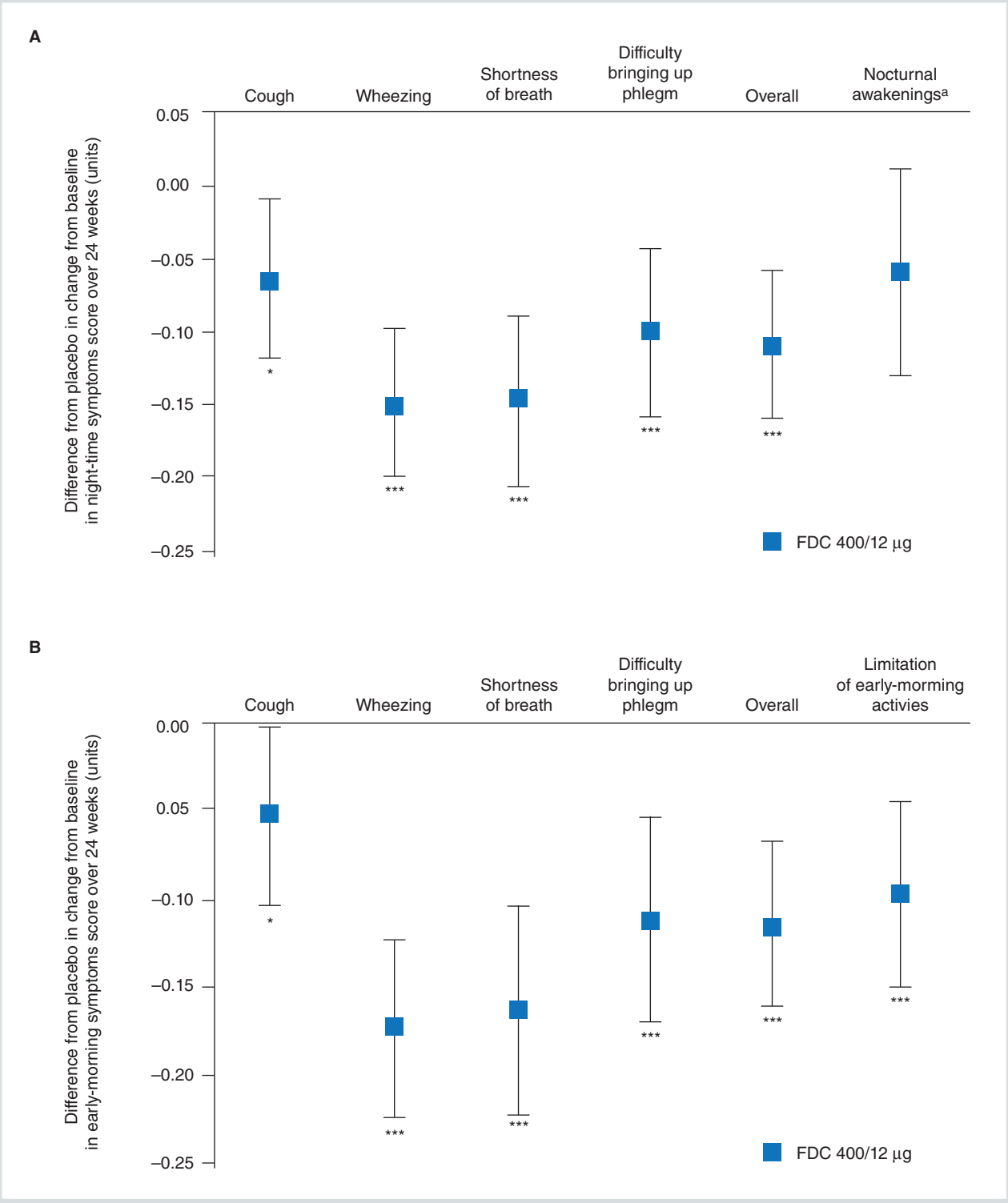

Figure 4. Difference from placebo in change from baseline in symptom severity over 24 weeks. **A:** Night-time symptoms; **B:** early morning symptoms. Data are LS means differences from placebo +95% Cis; *p < 0.05, +++p < 0.001 versus placebo *(reproduced with permission from Bateman ED et al.[78]).*

CI: confidence interval; FDC: aclidinium/formoterol fixed-dose combination; LS: least square.

data could suggest a positive effect. The Spanish population included in the ASSESS study was less symptomatic than the remaining European population, with better sleep quality and HRQoL[15]. These differences were observed despite presenting a similar degree of airflow limitation. Although the reasons why Spanish patients were less symptomatic remain to be properly established, up to 70% of the Spanish patients were treated with triple therapy, the results of which were significantly higher than 47% of the European patients. It should be noted that there was more activity and a higher proportion of men among the Spanish cases[15].

CONCLUSIONS

In-between exacerbations, COPD is usually regarded as a stable condition, but now there is a large body of evidence that respiratory symptoms vary in this state. This symptom variability is present in approximately half of COPD patients. The early morning was the worst period of time referred by patient, but the nighttime period is also considered important. Dyspnoea was the most frequently symptom and its perception was associated with a limitation of morning activities. Severity of the disease or previous exacerbation history are also risk factors associated with the variation of the symptoms, but even mild or non-exacerbated patients also showed variability. This time-dependent variability has important consequences, since it has an impact on life activities, sleep quality, exacerbations or HRQoL. In a way, this can bring an opportunity to further identify symptoms and treat them more properly to improve the outcomes.

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REFERENCES

1. Soriano JB, Calle M, Montemayor T, Alvarez-Sala JL, Ruiz-Manzano J, Miravitlles M. The general public's knowledge of chronic obstructive pulmonary disease and its determinants: current situation and recent changes. Arch Bronconeumol. 2012;48:308-15.
2. Global Strategy for the Diagnosis, Management and Prevention of COPD. Available from: http://www. goldcopd.org. Accessed 15 December 2019.
3. Guía de práctica clínica para el diagnóstico y tratamiento de pacientes con enfermedad pulmonar obstructiva crónica (EPOC) – Guía Española de la EPOC (GesEPOC). Versión 2017. Arch Bronconeumol. 2017;53 :Supl 1:1-52
4. Seemungal TAR, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157:1418-22.
5. Crook S, Büsching G, Keusch S et al. The association between daily exacerbation symptoms and physical activity in patients with chronic obstructive pulmonary disease. Int J Chron Obstr Pulmon Dis. 2018:13:2199-2206.
6. Wilkinson TMA, Patel IS, Vilks M, Donaldson GC, Wedzicha JA. Airway bacterial load and FEV1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;167:1090-5.
7. Soler-Cataluña JJ, Martínez-Garcia MA, Román Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronico obstructive pulmonary disease. Thorax. 2005;60:925-31.
8. Clark TJ: Diurnal rhythm of asthma. Chest. 1987;91:Suppl 6:137S-41S.
9. 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;25:2043-8.
10. Kessler R, Partridge MR, Miravitlles M, Cazzola M, Vogelmeier C, Leyanud D, Ostinelli J. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J. 2011;37:264-72.

11. Espinosa de los Monteros MJ, Peña C, Soto Hurtado EJ et al. Variability of respiratory symptoms in severe COPD. Arch Bronconeumol. 2012;48:3-7.
12. Roche N, Chavannes NH, Miravitlles M. COPD symptoms in the morning: impact, evaluation and management. Respir Res. 2013;14:112.
13. Lopez-Campos JL, Calero C, Quintana-Gallego E. Symptom variability in COPD: a narrative review. Int J Chron Obstruct Pulmon Dis. 2013;8:231-8.
14. Miravitlles M, Worth H, Soler-Cataluña J 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.
15. Soler-Cataluña JJ, Sauleda J, Valdés L et al. Prevalencia y percepción de la variabilidad diaria de los síntomas en pacientes con enfermedad pulmonar obstructiva crónica estable en España. Arch Bronconeumol. 2016;52:308-15.
16. Miravitlles M, Izquierdo JL, Esquinas C et al. Respir Med 2017;129:165-72.
17. Lu M, Wang X, Cai B et al. Perception of circadian variation of symptoms in Chinese patients with chronic obstructive pulmonary disease. J Thorac Dis. 2017;9:3888-95.
18. Kim MA, Suh MK, Park J et al. Impact of symptom variability on clinical outcomes in COPD: analysis of a longitudinal cohort. Int J Chron Obstruct Pulmon Dis. 2019; 14:2135-44.
19. 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.
20. Guberan E, Williams MK, Walford J, Smith MM. Circadian variation of FEV1 in shift workers. Br J Ind Med. 1969; 26:121–5.
21. Nadel JA, Barnes PJ. Autonomic regulation of the airways. Annu Rev Med. 1984. 35:451–67.
22. 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;58:855-60
23. Spengler CM, Shea SA. Endogenous circadian rhythm of pulmonary function in healthy humans. Am J Respir Crit Care Med. 2000;162:1038–46.
24. van Noord JA, Aumann JL, Janssens Eet al. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. Chest. 2006;129:509–17.
25. McCarley C, Hanneman SK, Padhye N, Smolensky MH. A pilot home study of temporal variations of symptoms in chronic obstructive lung disease. Biol Res Nurs. 2007;9:8–20.
26. Sundar IK, Yao H, Sellix MT, Rahman I. Circadian molecular clock in lung pathophysiology. Am J Physiol Lung Cell Mol Physiol. 2015;309:L1056-75.
27. Parish JM. Sleep-related problems in common medical conditions. Chest. 2009; 135:563–72.
28. Weitzenblum E, Chaouat A. Sleep and chronic obstructive pulmonary disease. Sleep Med Rev. 2004;8:281–94.
29. Lewis DA. Sleep in patients with asthma and chronic obstructive pulmonary disease. Curr Opin Pulm Med. 2001;7:105–12.
30. Owens RL, Malhotra A. Sleep-disordered breathing and COPD: the overlap syndrome. Respir Care. 2010;55:1333–44
31. Marrone O, Salvaggio A, Insalaco G. Respiratory disorders during sleep in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2006; 1:363–72.
32. Mueller PT, Gomes MD, Viegas CA, Neder JA. Systemic effects of nocturnal hypoxemia in patients with chronic obstructive pulmonary disease without obstructive sleep apnoea syndrome. J Bras Pneumol. 2008;34:567–74.
33. Gilmartin GS, Tamisier R, Curley M, Weiss JW. Ventilatory, hemodynamic, sympathetic nervous system, and vascular reactivity changes after recurrent nocturnal sustained hypoxia in humans. Am J Physiol Heart Circ Physiol. 2008; 295:H778–85
34. Turner-Warwich M. Epidemiology of nocturnal asthma. Am J Med. 1988; 85:6-8.
35. Hetzel MR, Clark TJ. Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. Thorax. 1980:35:732-8.
36. McNicholas WT. Impact of sleep in COPD. Chest. 2000;117 (2 Suppl):48S-53S.
37. Cormick W, Olson LG, Hensley MJ, Saunders NA. Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. Thorax. 1986;41:846-54.
38. Agustí A, Hedner J, Marin JM, Barbé F, Cazzola M, Rennard S. Nighttime symptoms: a forgotten dimension of COPD. Eur Respir Rev. 2011; 20:183-94.
39. Stephenson JJ, Cai Q, Mocarski M, Tan H, Doshi JA, Sullivan D. 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.
40. Pokrzywinski RF, Meads DM, McKenna SP, Glendenning GA, Revicki DA. Development and psychometric assessment of the COPD and Asthma Sleep Impact Scale (CASIS). Health Qual Life Outcomes. 2009;7:98.
41. Partridge MR, Miravitlles M, Ståhl E, Karlson N, Svensson K, Welte T. Development and validation of the Capacity of Daily Living during the Moring questionnaire and the Global Chest Symptoms Questionnaire in COPD. Eur Respir J. 2010;36:96-104.
42. Marin JM, Beeh KM, Clemens A et al. Early bronchodilator action of glycopyrronium versus tiotropium in moderate-to-severe COPD patients: a cross-over blinded randomized study (Symptoms and Pulmonar function in the morning). Int J Chron Obstruct Pulmon Dis. 2016;1425-34.
43. van Buul AR, Kasteleyn MJ, Chavannes NH, Taube C. Physical activity in the morning and afternoon is lower in patients with chronic obstructive pulmonary disease with morning symptoms. Respir Res. 2018;19:49.
44. A. Hareendran, A.C. Palsgrove, M. Mocarskiet al. The development of a patient-reported outcome measure for assessing nighttime symptoms of chronic obstructive pulmonary disease, Health Qual. Life Outcomes. 2013;11:104.
45. M. Mocarski, E. Zaiser, D. Trundell, B.J. Make, A. Hareendran, Evaluation of the psychometric properties of the nighttime symptoms of COPD instrument, Int. J. Chron Obstruct Pulmon Dis. 2015:10:475-87.
46. Fisher P, Gross V, Kroening J et al. Description of nighttime cough epochs in patients with stable COPD GOLD II-IV. Int J Chron Obstruct Pulmon Dis. 2018;1071-78.
47. Summer H, Woodcock A, Kolsum U et al. Predictors of objetctive cough frequency in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187:943-9
48. Nuñez A, Esquinas C, Barrecheguren M, Calle M, Casamor R, Miravitlles M. Evaluation the impact of morning symptoms in COPD using the Capacity of Daily Living during the Morning (CDLM) questionnaire. Int J Chron Obstruc Pulmon Dis. 2018;13:3837-44.
49. Nicola S, Incalzi A, Blasi F et al. Circadian rhythm of COPD symptoms in clinically based phenotypes. Results from the STORICO Italian observational study. BMC Pulm Med. 2019;19:171.
50. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;16:1608-13.
51. Rodriguez-Roisin R. Towards a consensus definition for COPD exacerbation. Chest. 2000; 117:398S-401S.
52. Langsetmo L, Platt RW, Ernst P, Bourbeau J. Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. Am J Respir Crit Care Med. 2008;177:396-401
53. Soler-Cataluña JJ, Alcázar B, Miravitlles M. The concept of control of COPD in clinical practice. Int J Chron Obstruct Pulmon Dis. 2014; 9:1397-1405.
54. Soler-Cataluña JJ, Alcazar-Navarrete B, Miravitlles M. The concept of control in COPD: a new proposal for optimising therapy. Eur Respir J. 2014;44:1072-5.
55. Soler-Cataluña JJ, Marzo M, Catalán P, Miralles C, Alcazar B, Miravitlles M. Validation of clinical control in COPD as a new tool for optimizing treatment. Int J Chron Obstruct Pulmon Dis. 2018;13:3719-31.
56. 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; 34:648-54
57. Van der Molen T, Willemse BWM, Schokker S, ten Hacken NHT, Postma DJ, Juniper EF. Development, validity and responsiveness of the clinical COPD questionnaire. Health Qual Life Outcomes. 2003;1:13

58. Nibber A, Chisholm A, Soler-Cataluña JJ, Alcazar B, Price D, Miravitlles M. on behalf of the Respiratory Effectiveness Group. Validating the concept of COPD control: a real-world cohort study from the United Kingdom. COPD. 2017;14: 504-12.
59. Miravitlles M, Sliwinski P, Rhee CK et al. Evaluation criteria for clinical control in a prospective, international, multicenter study of patients with COPD. Respir Med. 2018;136:8-14
60. Soler-Cataluña JJ, Alcázar B, Marzo M, Pérez J, Miravitlles M. Evaluation of changes in control status in COPD: an opportunity for early intervention: control status is useful for clinical assessment. Chest. 2019. Doi: 10.1016/j.chest.2019.11.004
61. Soler-Cataluña JJ, Alcázar B, Miravitlles M. Clinical control in COPD: A new therapeutic objective?. Arch Bronconeumol. 2019;doi: 10.1016/j.arbres. 2019 .06.004.
62. Muñoz A, Small M, Wood R, Ribera A, Nuevo J. The impact of morning, daytime, and nighttime symptoms on disease burden in real-world patients with COPD. Int J Chron Obstruc Dis. 2018;13:1557-68.
63. van Buul AR, Kasteleyn MJ, Chavannes NH, Taube C. Association between morning symptoms and physical activity in COPD: a systematic review. Eur Respir Rev. 2017;26:160033.
64. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J. 2009;33:262–72.
65. Gimeno-Santos E, Frei A, Steurer-Stey C et al. PROactive consortium. Determinants and outcomes of physical activity in patients with COPD: a systematic review. Thorax .2014;69:731-9.
66. Miravitlles M, Worth H, Soler-Cataluña JJ et al. The relationship between 24-hour symptoms and COPD exacerbations and healthcare resources use: results from an observational study (ASSESS). COPD. 2016;13:561-8.
67. van der Molen T, Miravitlles M, Kocks JW. COPD management: role of symptom assessment in routine clinical practice. Int J Chron Obstruct Pulmon Dis. 2013;8:461–71.
68. Price D, Small M, Milligan G, Higgins V, García Gil E, 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.
69. Partridge MR, Schuermann W, Beckman O, Persson T, Polanowski T. Effect on lung function and morning activities of budesonide/ formoterol versus salmeterol/fluticasone in patients with COPD. Ther Adv Respir Dis. 2009; 3:1-11.
70. Welte T, Miravitlles M, Hernandez P et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180: 741-50.
71. Di Marco F, Santus P, Scichilone N et al. Symptom variability and control in COPD: advantages of dual bronchodilation therapy. Respir Med. 2017;49-56.
72. McNicholas WT, Calverley PM, Lee A et al. Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD. Eur Respir J. 2004;23:825–31.
73. Martin RJ, Bartelson BL, Smith P et al. Effect of ipratropium bromide treatment on oxygen saturation and sleep quality in COPD. Chest. 1999;115:1338–45.
74. Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease, Respir Res. 2013;14: 49.
75. Buhl R, Maltais F, Abrahams R et al. Tiotropium and olodaterol fixed-dosse combination versus mono-components in COPD (GOLD 2-4). Eur Respir J. 2015; 5:969-79.
76. Chapman KR, Bateman ED, Chen H, Hu H, Fogerl R, Banerji D. QVA 149 improves lung function, dyspnea, and health status independent of previously prescribed medications and COPD severity: a subgroup analysis from the SHINE and ILLUMINATE studies. Chronic Obstr Pulm Dis. 2015; 248-60.
77. Donohue JF, Niewoehner D, Brooks J, O'Dell D, Church A. Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. Respir Res. 2014; 15:78.
78. Bateman ED, Chapman KR, Singh D et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). Respir Res. 2015;16:92.