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An Observational Study To Characterize 24 – Hour COPD Symptoms And Their Relationship With Patient -Reported

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Abstract
Few studies have investigated the 24-hour symptom profile in patients with COPD or how symptoms during the 24-hour day are inter-related. This observational study assessed the prevalence, severity and relationship between night-time, early morning and daytime COPD symptoms and explored the relationship between 24-hour symptoms and other patient-reported outcomes.

INTRODUCTION

Despite being preventable and treatable, chronic obstructive pulmonary disease (COPD) is associated with considerable morbidity and mortality [1],[2] and its prevalence is expected to increase in the coming decades [3]. The characteristic symptoms of COPD include breathlessness, cough and increased sputum production and, based on cohort studies, there is now extensive evidence that COPD symptoms have a considerable impact on patients' daily activities, health status and quality of life [4]-[8]. Furthermore, while COPD is diagnosed clinically based on persistent airflow limitation, it is the impact of symptoms on patients' daily lives that generally drives them to seek a diagnosis. The importance of considering COPD symptoms in the overall assessment of COPD, and in determining appropriate treatment approaches, is now recognised [9]. Reducing symptoms, improving health status and increasing physical activity are major goals in the management of stable COPD [9].COPD symptoms have been reported to vary throughout the day [10]-[12]. In cohort studies, patients with COPD who were receiving ongoing treatment with their normal COPD medication reported that their symptoms were worst in the morning [10],[12]. Morning symptoms impact on patients' normal activities [8],[10],[12],[13] and have been demonstrated to be associated with worse health status and a higher risk of COPD exacerbations [8],[13]. In the working population, morning symptoms were also significantly associated with increased annual absenteeism [13]. With regard to night-time symptoms, a recent real-world study also demonstrated that patients with night-time symptoms had significantly worse health status, more sleep disturbances and higher healthcare resource utilisation than patients without night-time symptoms [7].In a pan-European, observational study, patients' perception of the variability of their breathlessness was associated with both the severity of breathlessness and frequent exacerbations [10], while the pattern of COPD symptom variability has been shown to be influenced by disease severity [12]. Previous studies have also shown an association between morning or night-time symptoms and reduced lung function [7],[13],[14]. However, the association between symptoms in each part of the 24-hour day and the severity of airflow obstruction and the inter-relationship between 24-hour COPD

symptoms has not previously been investigated in a single patient cohort.In this observational study, we investigated the prevalence and severity of night-time, early morning and daytime symptoms in patients with stable COPD being treated in clinical practice and explored the relationship between symptoms in each part of the 24-hour day. Additionally, to better understand the relationship between 24-hour symptoms and other aspects of a patient's overall well-being, we assessed their association with the severity of airflow obstruction and other patient-reported outcomes, including self-perceived dyspnoea, health status, anxiety and depression levels, sleep quality and physical activity level.

RATIONALE

Few studies have investigated the 24-hour symptom profile in patients with COPD or how symptoms during theS 24-hour day are inter-related. This observational study assessed the prevalence, severity and relationship between night-time, early morning and daytime COPD symptoms and explored the relationship between 24-hour symptoms and other patient-reported outcomes**.**

STUDY AIM AND OBJECTIVE

AIM

The study is design for characterise 24-hour COPD symptoms and their relationship with patients reported outcomes

OBJECTIVES

1.To assess the 24 hours copdsymptoms (during morning and night time)

2.Elabrate the characterise the 24 hours copd symptoms and their relationship with patients report

HYPOTHESIS

H0: There is no significant the characterise the 24 hours copd symptoms and their relationship with patients report

H1: There is a significant the characterise the 24 hours copd symptoms and their relationship with patients report

METHODOLOGY

Study design : observation study (case control study)

Study location : The Study will be conducted in an urban area of Salem Tamil Nadu, India.

Study participants:

The Adult participants aged 20 years to 70 years who are living in urban area of Salem will be included in the study . The study samples will be selected keeping in view of following predetermined criteria.

INCLUSION CRITERIA:

- Patient above 20 years to 70 years will be included.
- Patient living in urban area of Salem , Tamil Nadu.
- Patients with emphysema, bronchitis
- Chronic obstructive pulmonary patients who are willing to participate in this study.
- Those who are able to understand and speak Tamil.

EXCLUSION CRITERIA:

- Patient who are critical condition .
- Using any other complementary treatment.
- Who were absent at the time of data collection .
- Children will be excluded from the study .
- Patient who are not willing to participate will be excluded.

STUDY DESIGN

This was a multinational, non-interventional, observational study conducted in 85 clinical practice centres (pulmonologists outpatients and primary care) across Denmark, France, Germany, Italy, The Netherlands, Spain, Sweden and UK (see Additional file 1 for a list of investigators). Patients who met the eligibility criteria were identified consecutively at each site, with each site having a maximum quota to minimise selection bias. The study consisted of a baseline visit (Day 1) and a follow-up telephone interview after 6 months. There were no interventions beyond routine clinical care delivered at the discretion

Study population

Patients were aged ≥40 years with mild to very severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric classification [15], (spirometry data from the year before baseline were considered valid). Patients were current or former smokers with a smoking history of ≥10 pack-years and had no history of COPD exacerbation in the previous month.

Exclusion criteria were: any change in maintenance COPD treatment in the previous 3 months; a previous diagnosis of asthma, sleep apnoea syndrome or chronic respiratory disease other than COPD; and any acute or chronic condition that would limit the patient's ability to complete the questionnaires.

ETHICAL CONSIDERATION

The Participant will be selected who match the inclusion criteria of this study. Explanation given to them about project aims and methodology and seek their consent to participate in the study .Only those providing informed consent will be recruited into the study .Throughout the study period ,a strict ethical code of practice will be followed for the experimental of personal information using the study tool of scales.

LITERATUE REVIEW

Collins EG, et al(2003), conducted a study regarding breathing pattern retaining and exercise in persons with chronic obstructive pulmonary disease . They used a method in pulmonary rehabilitation to help alleviate the symptoms of dyspnea endured by people who suffer from airflow obstructive secondary to chronic obstructive pulmonary disease (COPD), Other techniques such as biofeedback also have been successfully used. The article described the altered breathing pattern used by patients with COPD at rest and during physical activity. The literature is reviewed regarding techniques of breathing pattern retraining that have been developed to improve the capacity of persons with COPD to performs activities of daily living, a primarily rehabilitation outcomes.

Ritz T, et al (1997)conduced a review of the behavior interventions in asthma and breathing training. And the review found that the systematic documenting in the benefits of these techniques in asthma

patients. The physiological rationale of abdominal breathing in asthma is not clear, and adverse effects have been reported in chronic obstructive status. Theoretical analysis and empirical observation suggest positive effects of pursed-lip breathing and nasal breathing but clinical evidence is lacking. Modification of breathing and nasal breathing patterns along does not yield any significant benefit. There is limited evidence that inspiratory muscle training and hypoventilation training can help reduce medication consumption, in particular beta-adrenergic inhaler use. Breathing exercise do not seem to have any substantial effect on parameters of basal lung function. They individual breathing technique in asthma, differential effect in sub-group of asthma patients, and the generalization of training effect on daily life.

Nihon kokyuki Gakkai Zasshi et al (1996) conducted a study to evaluate the effects of a short term pulmonary rehabilitation program on dyspnea, exercise capacity, and lung function . 15 patients with chronic respiratory failure due to pulmonary emphysema were enrolled in such a program for 3 week as inpatient. The program consisted of pursed lip breathing , respiratory muscle stretch gymnastics , and walking with synchronized breathing. The results had shown that dyspnea as measured with a visual analogue scale at the end of a 6-minte walk before and after the program (49.7 +/- to 24.2 +/- 3.8%) decreased significantly ($p<0.01$) . As a measure of functional exercise capacity, the 6-minute walking distance (226.9 +/- 32.4 m to 292.1 +/- 35.8 m) increased significantly ($p<0.01$). As an indicator of maximal exercise capacity ,endurance time on an incremental treadmill test did not improve. Spiro metric data did not change during the study . Total lung capacity (TLC) (8.44 +/- 0.70 L to 7.58 +/- 0.74 L) and residual volume (RL) (5.13+/- 0.53L to 4.28 +/- 0.59L) decreased significantly ($p<0.01$). The findings suggest that this program relieves dyspnea , increases the functional capacity and decrease the functional exercise capacity , and decrease TLC and RV on patients with chronic respiratory failure due to pulmonary emphysema.

Sutbyaz ST,et al (1996) conducted a study to determine whether two types of exercise-breathing retraining (BRT) and inspiratory muscle training (IMT)-improve on cardiopulmonary functions and exercise tolerance in patients with stroke. They used a randomized controlled trial techniques in which forty-five in patients with stroke (24 men, 21 women) were recruited for the study. The subjects were randomized into three groups : 15 assigned to receive inspiratory muscle training (IMT); 15 assigned to a control group. All study groups participated in a convential stroke rehabilitation programme. Each subject underwent pulmonary function and cardiopulmonary exercise tests. The results shown that after the training programme, the IMT group had significantly improved forced expiratory volume at 1 second (FEV(1)), forced vital capacity (FEV) , vital capacity (VC) , forced expiratory flow rate 25-75 % (FEEF 25-75%) and maximum voluntary ventilation (MVV) values compound with the BRT and control groups, although there were no significant differences between the BRT and control group ($p<0.01$), Peak expiratory flow rate (PEF) Value was increased significantly in the BTR group compared with the IMT and control groups. The IMT group also had significantly higher peak oxygen consumption (VO (2 peak)) than the BRT and control groups, ($p<0.001$).There was a statiscally significant increase in maximum inspiratory pressure (PI (max)) and maximum inspiratory and expiratory pressure (PE(max)) in the BRT group and ,PI (max)in the IMT group compared with baseline and the control group.In the IMT group, this was associated with improvement in exercise capacity, sensation of dyspnea and quality of life.

Breslin EH, et al (1994) conduced the study to indicate a change in the pattern of chest wall muscle recruitment and improved ventilation with pursed –lip breathing (PLB) in COPD.Pursed-lip breathing

(PLB) led to increased rib cage and accessory muscle recruitment during inspiration and expiration ,increased abdominal muscle recruitment during expiration, decreased duty cycle of the inspiratory muscles and respiratory rate, and improved Sao2.In addition ,PLB resulted in no changes in pressure across the diaphragm.Changes in chest wall muscle recruitment and respiratory temporal parameters concomitant with increased Sao2 indicate a mechanism of improving ventilation with PLB while protecting the diaphragm from fatigue in COPD. Alterations in the pattern of respiratory muscle recruitment with PLE may be associated also with the amelioration of dyspnea, The study suggested further investigation is necessary to explore the relationship between the pattern of respiratory muscle recruitment during PLB and dyspnea.

Van der Schans CP ,et al(1992) conducted a study to assess the effect of breathing with a positive expiratory pressure of 5 cm H2O , simulating pursed lips breathing (SPLB), on respiratory muscle activity and pulmonary function during induced airway obstruction. In twelve asthmatic patients, tonic and phasic electromyography (EMG) activity of the following muscles was obtained: scalence muscle, parasternal muscle , and abdominal msuscles, pulmonary function and EMG measurement were performed before and after propranolol induced airway obstruction . The results shown that simulated pursed lips breathing resulted in a significant increase of functional residual capacity and tidal volume both at baseline and during airway obstruction. Phasic respiratory muscle activity during PEP breathing increased especially at baseline. It shown the beneficial effects of breathing with a positive expiratory pressure 5cm H2O , which is smilar to pursed lips breathing , cannot be explained by changes in respiratory muscle activity or pulmonary function.

Das S,Mukherjee S,ET AL (1992) A pre-experimental study was conduced on breathlessness in patients with COPD . The twenty two patients with mild to severe COPD were studied . Dyspnea was assessed by a Modified Borg Scale.The patients with deep breathing exercise exhibited a significant reduction in end expiratory volume of chest wall and reduce breathlessness. They study showed that deep breathing exercise are more effective in reducing in COPD patients. Dyspnea and rest and dring exercise in COPD. The eight COPD patients (6 male and 2 female) with a mean age of 11 years . Deep breathing exercise promated a slower and deeper breathing pattern both at rest and during exercise.Deep breathing have a variable effect on dyspnea when performed voliticully during exercise by patient with COPD .The study showed effectiveness of deep breathing exercise in patient at rest.

Minas M,ET AL (1992) A experimental study was conducted on the impact of deep breathing exercise on breathing pattern and dyspnea in severe COPD patients. The subjects of the study were 125 patients.This study shows deep breathing exercise is effective in improving breathing pattern and in patient with COPD .A cohort study was conducted on efficient integrated education for older patients with COPD using deep breathing exercise. A total of 85 patients . This study shows integrated education for older patients with COPD effectively improved patients deep breathing exercise.

breathing exercise in COPD. A randomized controlled clinical trail.145 subjects were included among them 100 mens and 45 women , Deep breathing exercise is well tolerated in COPD and significantly improve dyspnea randomized controlled trail study was conducted on hospital based physiotherapeutic exercise in COPD self management among 142 patients. Out of which 74 intervention and 68 control patients were included . This study demonstrates that a hospital based re activation programme improves exercise capacity in patient with moderately and severe COPD. Exercise tolerance capacity is more in COPD patients.A Study was conducted on the effectiveness of deep breathing exercise in managing breathless in respiratory illness. 220 subjects were included and the study revealed that

breathlessness isa debilitating and distressing symptoms to manage. Therefore , deep breathing exercise was one of the effective non pharmacological intervention in treating dyspnea .

Izadi-avanji FS ,ET AL (1990) A true experimental study was conducted on deep breathing exercise on dysphea in moderate COPD patients.The subjects of the study were 240 . Out of which 120 subjects were manipulated and the rest were getting no intervention. According to the study ,it revealed that were considerably more effective to the subject given exercise rather than those without intervention .Thus it proved that deep breathing exercise was better than compared to other group.

An Observation Study To Assess The Potancy Of Deep Breathing Exercise Among Patients With Chronic Obstructive Pulmonary Disease Informed Consent

Study Title:

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

		Please initial box (Subject)
(i)	I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.	
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
(iii)	I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	
(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	
(v)	I agree to take part in the above study	

Signature (or Thumb impression) of the

Subject / Legally Acceptable Representative:
Date: __ /__ / ____
Signatory's Name: _____

Signature of the Investigator: _____ Date: __ /__ / ____

Study Investigator's Name: _____

Signature of the Impartial Witness _____ Date: __ /__ / ____

Name of the Impartial Witness: _____

நாள்பட்டநுரையீரல்அடைப்புநோயால்பாதிக்கப்பட்டநோயாளிகளிடையேஆழ்ந்தமூச்சுப்பயிற்சியின்ஆற்றலைமதிப்பிடுவதற்கானஒருகண்காணிப்புஆய்வு

படிப்புதலைப்பு:
ஆய்வுஎண்:
பாடத்தின்முதலெழுத்துகள்: _____
பாடத்தின்பெயர்: _____
பிறந்ததேதி / வயது: _____
தயவுசெய்துமுதலில்
பெட்டி (பொருள்)
(i) மேற்படிஆய்வுக்காக_____
தேதியிட்டதகவல்தாளைப்படித்துப்புரிந்துகொண்டுகேள்விகளைக்கேட்கும்வாய்ப்பைப்பெற்றுள்ளேன்என்பதைஉறுதிப்படுத்துகிறேன்.
(ii) ஆய்வில்நான்பங்கேற்பதுதன்னார்வமானதுஎன்பதையும், எனதுமருத்துவப்பராமரிப்புஅல்லதுசட்டஉரிமைகள்பாதிக்கப்படாமல், எந்தக்காரணமும்கூறாமல், எந்தநேரத்திலும்விலகிக்கொள்ளநான்சுதந்திரமாகஇருக்கிறேன்என்பதையும்புரிந்துகொள்கிறேன்.
(iii) மருத்துவபரிசோதனையின்ஸ்பான்சர், ஸ்பான்சரின்சார்பாகபணிபுரியும்மற்றவர்கள், நெறிமுறைகள்குழுமற்றும்ஒழுங்குமுறைஅதிகாரிகளுக்கு,
தற்போதையஆய்வுமற்றும்மேலும்எந்தஒருஆய்வும்சம்பந்தமாகஎனதுஉடல்நலப்பதிவுகளைப்பார்க்கஎனது அனுமதிதேவையில்லைஎன்பதைநான்புரிந்துகொள்கிறேன்.
நான்விசாரணையில்இருந்துவிலகியிருந்தாலும், அதுதொடர்பாகநடத்தப்படலாம். இந்தஅணுகலைநான்ஒப்புக்கொள்கிறேன். இருப்பினும், மூன்றாம்தரப்பினருக்குவெளியிடப்படும்அல்லதுவெளியிடப்படும்எந்ததகவலிலும்எனதுஅடையாளம்வெளிப்படுத்தப்படாதுஎன்பதைநான்புரிந்துகொள்கிறேன்.
(iv)இந்தஆய்வில்இருந்துஎழும்எந்தவொருதரவுஅல்லதுமுடிவுகளின்பயன்பாட்டைக்கட்டுப்படுத்தவேண்டாம்என்றுநான்ஒப்புக்கொள்கிறேன், அத்தகையபயன்பாடுஅறிவியல்நோக்கத்திற்காக (கள்)
(v) மேற்கண்டஆய்வில்பங்கேற்கஒப்புக்கொள்கிறேன்

கையொப்பம் (அல்லதுகட்டைவிரல்பதிவு).

பொருள் / சட்டப்பூர்வமாகஏற்றுக்கொள்ளக்கூடியபிரதிநிதி:
தேதி: __ /___ / ____
கையொப்பமிட்டவரின்பெயர்: _____

புலனாய்வாளரின்கையொப்பம்: _____ தேதி: __ /__ / ____

ஆய்வுஆய்வாளரின்பெயர்: _____

பாரபட்சமற்றசாட்சியின்கையொப்பம்_____ தேதி: __ /___ / ____

பாரபட்சமற்றசாட்சியின்பெயர்: _____

DEMOGRAPHIC DATA
INTRODUCTION TO PARTICIPATE
Dear participations
This section of personal information and you are requested to answer the questions correctly the information collected from will be kept confidency.

DEMOGRAPHIC DATA
1.Name:
Age:
Sex: M/F
Address:
I.P/O.P.No:
Occupation:.
Economy class: High
Middle
Low

GENERAL DATA
1.How is your breathing today?
a)As usual b)Worse. c)Much worse. _____
2.Which is the colour of your sputum today?
a)As usual. b) Worse. c)Much worse. _____
3.Do you cough several times most day?
a)Yes. b)No. _____
4.RISK FACTORS AND TRIGGERS:
Smoking
Air Pollution like, Smoke / Fumes / Dust
Recurrent respiratory infection.
Atopy and Allergy
5.SMOKING HISTORY: ♦ Active ♦ Passive

Active:

♦ Cigarette / Cigar / Beedi

♦ Age at smoking started.

♦ Intensity of smoking in Pack-years.

Passive:

♦ Father / Husband / Son / Other (Specify Relation)

♦ Pack-year of smoking

6.PRESENTING SYMPTOMS: **DURATION**

a)Cough 1)3-6months

b)Cough with expectoration of sputum 2)6mnth-1yr

c)Breathlessness 3)More than 1 yr.

d)Wheeze

e)Chest pain

f)Fever

g)Haemoptysis

h)Both Legs Swelling

i)Others (Specify)

DYSPHENA DATA

1.Have you been repeatedly short of breath over the past 12 mnths? Response

a)Yes _____ 1 Eligible for breathlessness

b)No _____ 2 Screenout

2.How is your breathing today

a)As usual. b)Worse. c)Much worse

3.Are you using rescue medication/nebulizer or oxygen today?

a)No.b)As usual. c)More than usual. d)Much more than usual

4.Have you started with new prednisolone (a steroid used to treat various condition including breathing disorder) after last discharge?

a)Yes. b)No

5.How often do you Cough up phlegm (mucus membrane of the respiratory passages).

a)Almost never. b) Rarely. c) Sometimes. d) Frequently e)Very frequent

CONTACT DISEASE DATA

1.Previous History of

a)Asthuma b) Bronchitis c)Emphysema

2.Lung

a) inflammation ----------

b)excess mucus ----------

c) Alveolar membrane break down ----------

d) collapsed airway ----------

e)narrowed airway ----------

f) tight smooth muscle ----------

Results

Patients Of 743 patients who enrolled in the study and had a baseline visit, 727 were eligible for inclusion in the full analysis set. Demographics and baseline characteristics are shown in Table 1; 72.4% of patients had a diagnosis of moderate or severe COPD (based on severity of airflow limitation) and 58.9% had dyspnoea assessed on the mMRC scale as grade ≥2. Overall, 50.9% of patients were receiving treatment with triple therapy (long-acting β_2-agonists [LABA], long-acting muscarinic antagonists [LAMA] plus inhaled corticosteroids), with or without a phosphodiesterase 4 (PDE4) inhibitor (2.1% and 48.8%, respectively). In addition to COPD, 79.4% of patients had a comorbid medical condition; 45.1% of patients had a diagnosis of hypertension and 33.7% had cardiovascular disease. Based on physical activity level, 30.0% of patients were assessed as being sedentary, 38.1% as moderately active and 31.4% as active at baseline.

Table 1 Demographics and baseline characteristics

Characteristic	Eligible patients (N = 727)
Sex, n (%), male	478 (65.8)
Age, mean (SD), years (n = 725)	67.2 (8.8)
BMI, mean (SD), kg/m2 (n = 720)	26.4 (5.2)
Current smoker, n (%)	202 (27.8)
Smoking history, mean (SD), pack-years (n = 723)	43.1 (24.8)
Post-bronchodilator FEV1, mean (SD), L (n = 696)	1.4 (0.6)
% predicted FEV1, mean (SD) (n = 718)	52.8 (20.5)
COPD severity, n (%)	
GOLD group I (mild)	63 (8.7)
GOLD group II (moderate)	265 (36.5)
GOLD group III (severe)	261 (35.9)

GOLD group IV (very severe)	73 (10.0)
mMRC grade, mean (SD)	1.8 (1.0)
mMRCdyspnoea grade, n (%)	
0	53 (7.3)
1	244 (33.6)
2	244 (33.6)
3	140 (19.3)
4	44 (6.1)
Patients with an exacerbation in previous year, n (%)	392 (53.9)
Number of COPD exacerbations in previous year, mean (SD) (n = 724)	1.2 (1.6)
Current COPD medication, n (%)a	
LABAs + LAMAs + ICS	355 (48.8)
LABAs + ICS	100 (13.8)
LABAs + LAMAs	70 (9.6)
LABAs alone	66 (9.1)
LAMAs alone	50 (6.9)
Short-acting bronchodilatorsb	22 (3.0)
LABAs + LAMAs + ICS + PDE4 inhibitor	15 (2.1)
LAMAs + ICS	8 (1.1)
Otherc	19 (2.6)
No treatment	22 (3.0)

Total CAT score, mean (SD) (n = 721)	16.5 (8.1)
CAT score category, n (%)	
CAT score ≤10, n (%)	187 (25.7)
CAT score 11–20, n (%)	305 (42.0)
CAT score 21–30, n (%)	187 (25.7)
CAT score >30, n (%)	42 (5.8)
HADS anxiety score, mean (SD) (n = 710)	6.1 (4.2)
HADS depression score, mean (SD) (n = 714)	5.5 (4.1)
CASIS score, mean (SD) (n = 712)	44.1 (19.1)

n = patients with available data for each outcome; percentages are based on N = 727 patients.

[a]Used by >1% of patients.

[b]Includes: SABA alone; SABA + SAMA; SAMA alone.

[c]Includes: ICS alone; ICS + PDE4 inhibitor; LABA + ICS + PDE4 inhibitor; LAMA + LABA + PDE4 inhibitor.

BMI, body mass index; CASIS, COPD and Asthma Sleep Impact Scale; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; PDE4, phosphodiesterase 4; SABA, short-acting β_2 agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

Prevalence and severity of COPD symptoms in each part of the 24-hour day

The prevalence of COPD symptoms in each part of the 24-hour day is shown in Figure 1. In each part of the 24-hour day, >60% of patients experienced at least one COPD symptom in the week before baseline (Figure 1). Early morning and daytime symptoms were most common, however 63.0% of patients experienced at least one night-time symptom in the week before baseline and more than half of the patients (52.0%) reported having night-time symptoms at least three times during a typical week.

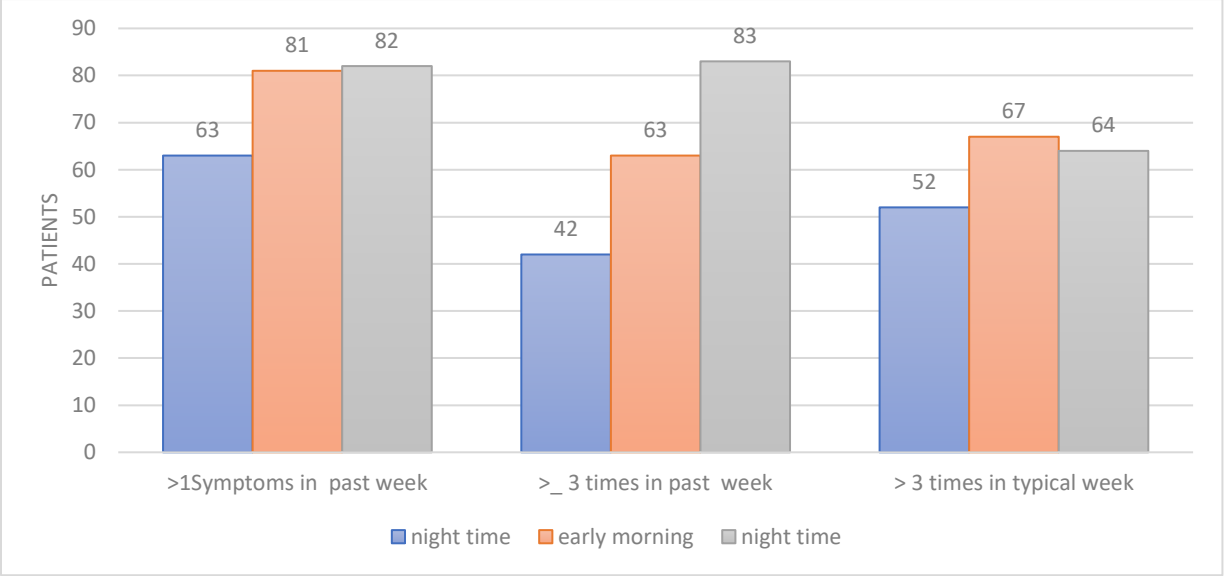


Fig.1 Prevalence and frequency of night-time, early morning and daytime COPD symptoms (N = 727).[a]A typical week refers to a week that the patient considered most usual for them during the previous month. COPD, chronic obstructive pulmonary disease.

Patients' assessment of the severity of their night-time, early morning and daytime symptoms is shown in Table 2. In symptomatic patients the overall severity of symptoms was comparable for the night-time, early morning and daytime periods (Table 2). In each part of the 24-hour day, most people assessed their symptoms during the previous week as mild or moderate (night-time 89.5%, early morning 87.9% and daytime 89.3%).

Table 2 Patients' assessment of night-time, early morning and daytime symptom severity in the week before baseline

Symptom severity	No. of patients (%)		
	Night-time	Early morning	Daytime
	(n = 409a)	(n = 571a)	(n = 589a)
Mild	191 (46.7)	252 (44.1)	254 (43.1)
Moderate	175 (42.8)	250 (43.8)	272 (46.2)
Severe	39 (9.5)	61 (10.7)	59 (10.0)
Very severe	4 (1.0)	8 (1.4)	4 (0.7)

Patients who reported symptoms during the previous week and provided data for symptom severity.COPD, chronic obstructive pulmonary disease.

Individual COPD symptoms

When individual symptoms were assessed, symptoms related to breathlessness were most common (71.4% of patients) followed by coughing (65.9%), bringing up phlegm or mucus (59.6%), wheezing (41.4%), chest tightness (32.9%) and chest congestion (23.4%). The frequency and pattern of each individual symptom varied throughout the 24-hour day (Figure 2). The proportion of patients reporting breathlessness increased from night-time through the morning and into the daytime, whereas coughing

and bringing up phlegm or mucus were most common early in the morning. Coughing and bringing up phlegm or mucus were the most common symptoms reported during the night-time

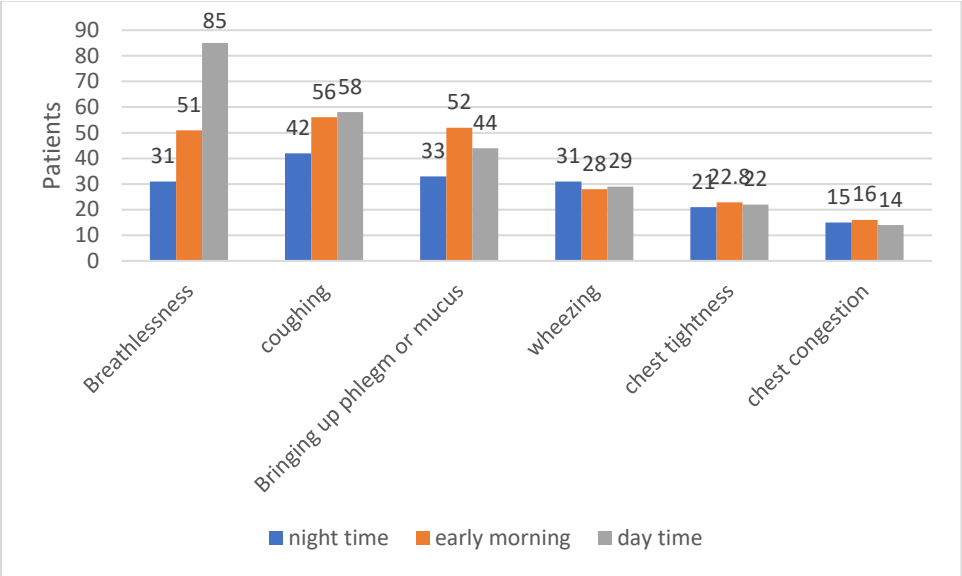


Fig.2 **Prevalence of individual COPD symptoms throughout the 24-hour day in the week before baseline (N = 300).** COPD, chronic obstructive pulmonary disease**.**

Relationship between COPD symptoms in each part of the 24-hour day

In the week before baseline, 90.5% of patients experienced COPD symptoms during at least one part of the 24-hour day (Figure 3). More than half of patients (56.7%) experienced symptoms throughout the whole 24-hour day; 10.6% of patients had symptoms in only one part (Figure 3). Almost 60% of patients had both night-time and early morning symptoms (Table 3). Among patients with night-time symptoms, 94.3% also had early morning symptoms while 73.3% of those with early morning symptoms also had night-time symptoms. A similar pattern was observed for the combinations of night-time and daytime symptoms (Table 3).

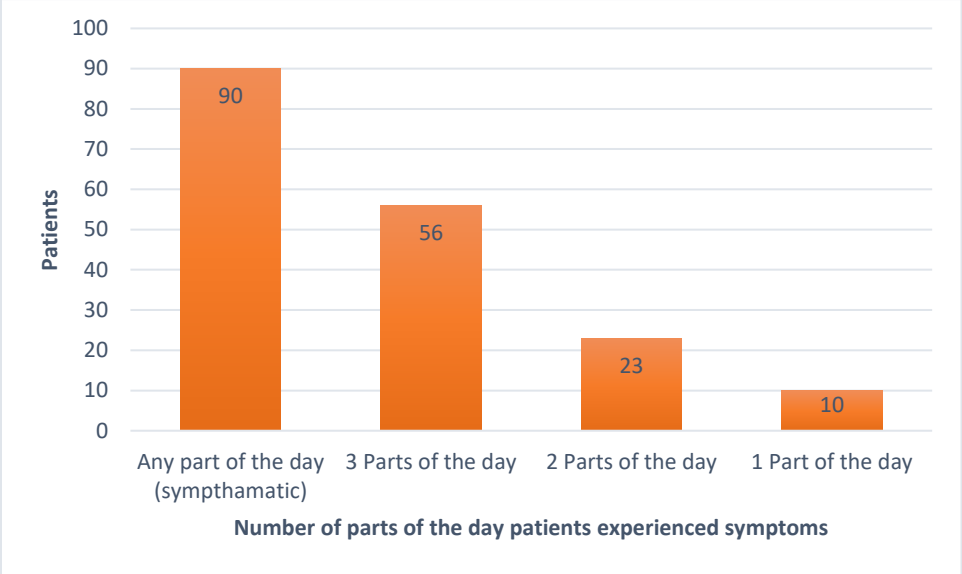


Fig.3 Prevalence of COPD symptoms during one, two or three parts of the 24-hour day in the week before baseline (N = 300). COPD, chronic obstructive pulmonary disease.

Table 3 Proportion estimates of night-time, early morning and daytime COPD symptom combinations

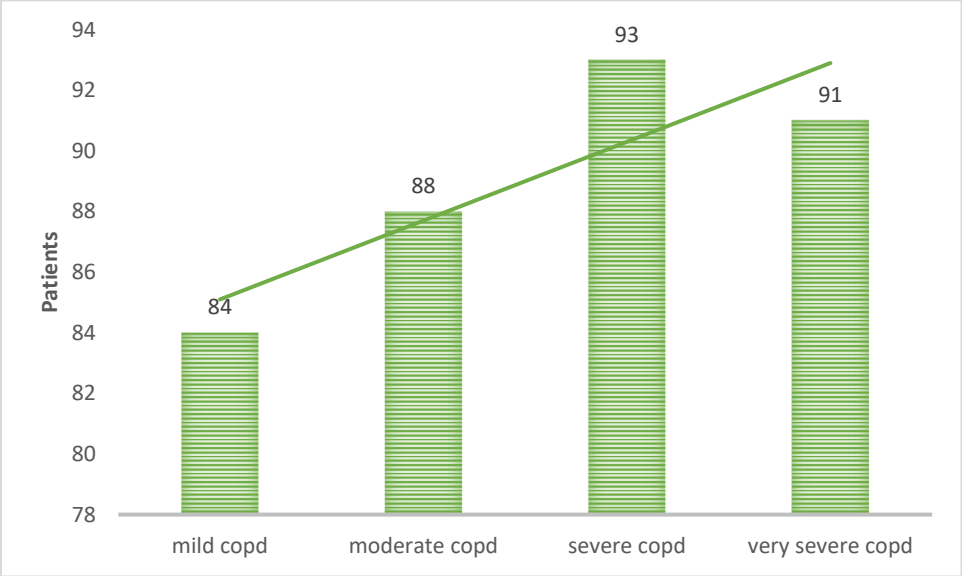
Symptom combinations	% (n/N)	[95% CI]
Night-time (NT) and early morning (EM) symptoms		
Overall patients with both NT and EM symptoms	59.8 (432/723)	56.1, 63.3
Patients with ≥1 NT symptom (n = 458) who also had ≥1 EM symptom	94.3 (432/458)	91.8, 96.1
Patients with ≥1 EM symptom (n = 589) who also had ≥1 NT symptom	73.3 (432/589)	69.6, 76.8
Night-time (NT) and daytime (DT) symptoms		
Overall patients with both DT and NT symptoms	59.4 (429/722)	55.8, 62.9
Patients with ≥1 NT symptom (n = 458) who also had ≥1 DT symptom	93.7 (429/458)	91.1, 95.6
Patients with ≥1 DT symptom (n = 598) who also had ≥1 NT symptom	71.7 (429/598)	68.0, 75.2
Early morning (EM) and daytime (DT) symptoms		
Overall patients with both EM and DT symptoms	75.0 (544/725)	71.7, 78.1
Patients with ≥1 EM symptom (n = 591) who also had ≥1 DT symptom	92.1 (544/591)	89.6, 94.0

Patients with ≥1 DT symptom (n = 601) who also had ≥1 EM symptom	90.5 (544/601)	87.9, 92.6

n = patients with available data for each combination.

When the relationships between symptoms during each part of the 24-hour day were assessed, there was a significant association for each potential symptom combination (night-time and early morning symptoms; night-time and daytime symptoms; and early morning and daytime symptoms; all $p < 0.001$). The relationships between night-time, early morning and daytime symptoms were maintained for all symptom combinations, irrespective of the severity of airflow limitation (mild to very severe all $p < 0.05$).

A)



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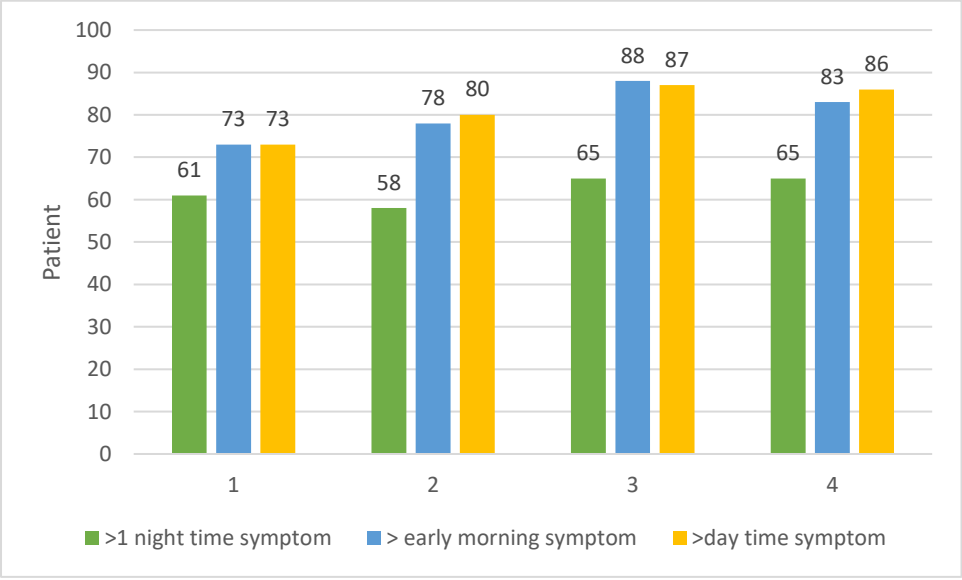


Fig.4 Prevalence of any COPD symptoms (A) overall and (B) during each part of the 24-hour day, according to COPD severity. n = patients in each group based on available data. COPD, chronic obstructive pulmonary disease.

There was a significant relationship between night-time, early morning and daytime symptoms and the severity of self-perceived dyspnoea (all p < 0.001; Table 4). Mean mMRC grades were significantly higher in patients with symptoms compared with patients without symptoms in each corresponding part of the 24-hour day (Table 4). There was also an association between the number of parts of the 24-hour day when patients experienced symptoms and dyspnoea severity (p < 0.001). Most patients who had grade ≥2 dyspnoea assessed on the mMRCdyspnoea scale had symptoms throughout the whole 24-hour day (63.8%); this compares with 46.5% of patients assessed as mMRC grade <2. There was no significant relationship between night-time, early morning or daytime symptoms and the presence of comorbidities in these patients.

Table 4 Patient-reported outcomes in patients with/without COPD symptoms during each part of the 24-hour day

	Night-tim+A107:C108 symptoms			Early morning symptoms			Daytime symptoms		
Patient-reported outcome	**No symptoms**	**≥1 symptom**	**p-value**	**No symptoms**	**≥1 symptom**	**p-value**	**No symptoms**	**≥1 symptom**	**p-value**
mMRC grade,	1.6	1.9	<0.001	1.4	1.9	<0.001	1.4	1.9	<0.001
mean (95% CI)	(1.5, 1.7)	(1.8, 2.0)		(1.2, 1.5)	(1.8, 2.0)		(1.2, 1.6)	(1.8, 2.0)	
	(n = 265)	(n = 457)		(n = 134)	(n = 591)		(n = 124)	(n = 600)	
CAT score,	11.6	19.3	<0.001	9.8	18.1	<0.001	10	17.9	<0.001
mean (95% CI)	(10.8, 12.4)	(18.6, 20.0)		(8.8, 10.9)	(17.4, 18.7)		(8.9, 11.1)	(17.3, 18.5)	
	(n = 263)	(n = 455)		(n = 133)	(n = 588)		(n = 124)	(n = 596)	
HADS anxiety score,	4.6	6.9	<0.001	4.1	6.5	<0.001	4.2	6.5	<0.001
mean (95% CI)	(4.1, 5.1)	(6.5, 7.3)		(3.4, 4.7)	(6.2, 6.9)		(3.5, 4.8)	(6.1, 6.8)	
	(n = 262)	(n = 445)		(n = 133)	(n = 577)		(n = 123)	(n = 586)	
HADS depression score,	4.2	6.2	<0.001	3.4	6	<0.001	3.7	5.9	<0.001
mean (95% CI)	(3.8, 4.6)	(5.8, 6.6)		(2.9, 4.0)	(5.6, 6.3)		(3.1, 4.4)	(5.5, 6.2)	
	(n = 263)	(n = 448)		(n = 132)	(n = 582)		(n = 123)	(n = 590)	
CASIS score,	33.6	50.2	<0.001	34.4	46.3	<0.001	34.2	46.2	<0.001
mean (95% CI)	(31.9, 35.2)	(48.4, 52.0)		(31.7, 37.1)	(44.8, 47.9)		(31.4, 37.0)	(44.7, 47.8)	
	(n = 260)	(n = 449)		(n = 131)	(n = 581)		(n = 122)	(n = 589)	

P values determined using Wilcoxon rank-sum test versus no symptoms in each period.n = patients with available data for each outcome.CASIS, COPD and Asthma Sleep Impact Scale; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council.

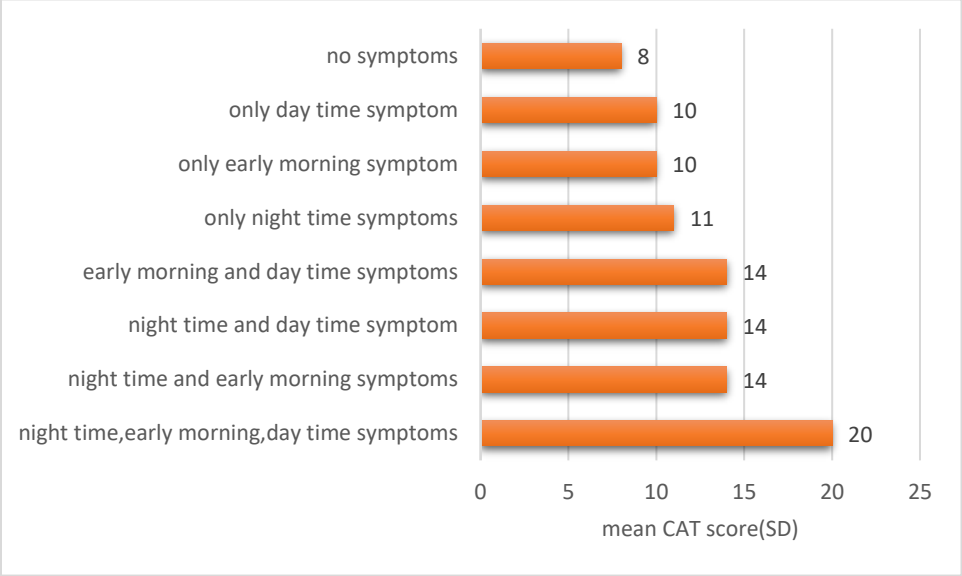
In each part of the 24-hour day, including night-time, there was a significant relationship between symptoms and health status, anxiety and depression levels, and sleep quality (all p < 0.001 versus no symptoms; Table 4). In each period, mean CAT scores were >7.5 points higher in patients with symptoms versus patients without symptoms (Table 4). Based on HADS score at baseline, 34.5% of patients had anxiety and 27.6% had depression. When assessed according to patients with and without symptoms in each part of the 24-hour day, mean HADS anxiety and depression scores were significantly higher in patients with symptoms versus those without symptoms (p < 0.001 for all; Table 4). Sensitivity analyses performed in patients with no medical history of anxiety (n = 534) or depression (n = 538) also

showed a significant association between symptoms and HADS anxiety and depression scores in each part of the 24-hour day (all $p < 0.001$). Patients with symptoms also had significantly higher CASIS scores compared with those without symptoms ($p < 0.001$ for all; Table 4), indicating greater sleep impairment. When patients who were receiving sleep medications or treatment for benign prostatic hyperplasia (n = 109) were excluded from the analyses of CASIS scores, the relationship between night-time, early morning and daytime symptoms and sleep quality remained significant in each period (data not shown).

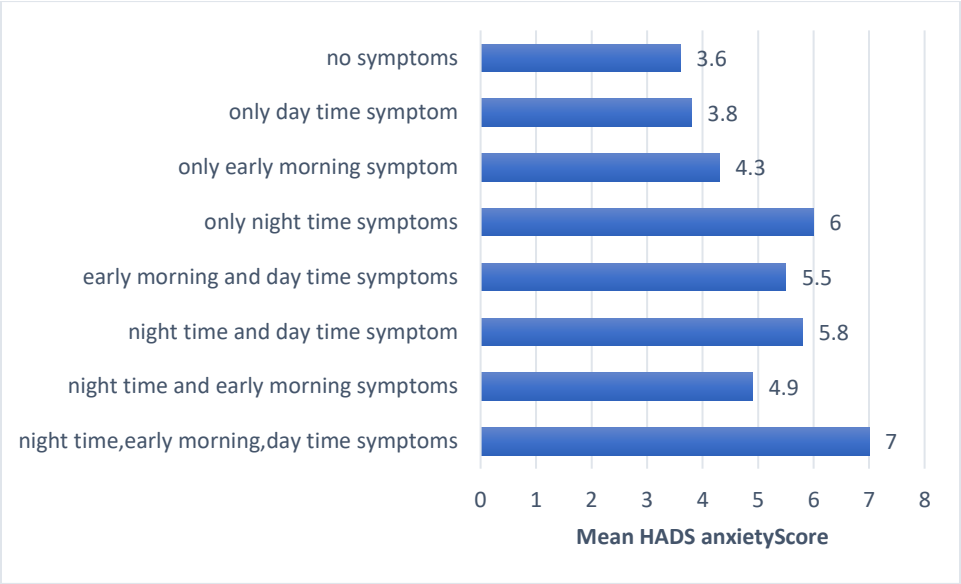
In each part of the 24-hour day, there was a significant relationship between symptoms and patients' physical activity level at baseline (assessed as sedentary, moderately active or active; $p < 0.05$ for each part of the 24-hour day). There was also a significant relationship for the number of parts of the 24-hour day when patients experienced symptoms and physical activity levels ($p = 0.006$). A higher proportion of patients who were sedentary had symptoms throughout the whole 24-hour day compared with patients who were active (64.2% versus 50.4%, respectively).

Mean CAT, HADS anxiety and depression, and CASIS scores according to each 24-hour symptom combination are shown in Figure 5. Patients with symptoms throughout the whole 24-hour day had the worst health status and sleep quality and the highest levels of anxiety and depression. CAT scores were higher in patients with symptoms during two or more parts of the 24-hour day than in patients with only night-time, early morning or daytime symptoms (Figure 5A). With the exception of patients with early morning and daytime symptoms, patients who reported night-time symptoms, either alone or in combination, had the highest anxiety levels (Figure 5B) and patients with any combination of early morning and night-time symptoms had the highest depression levels (Figure 5C). A similar pattern was generally observed when HADS scores were analysed in patients with no medical history of anxiety or depression (Additional file 3). Patients with any night-time symptoms had worse sleep quality than patients without night-time symptoms (Figure 5D).

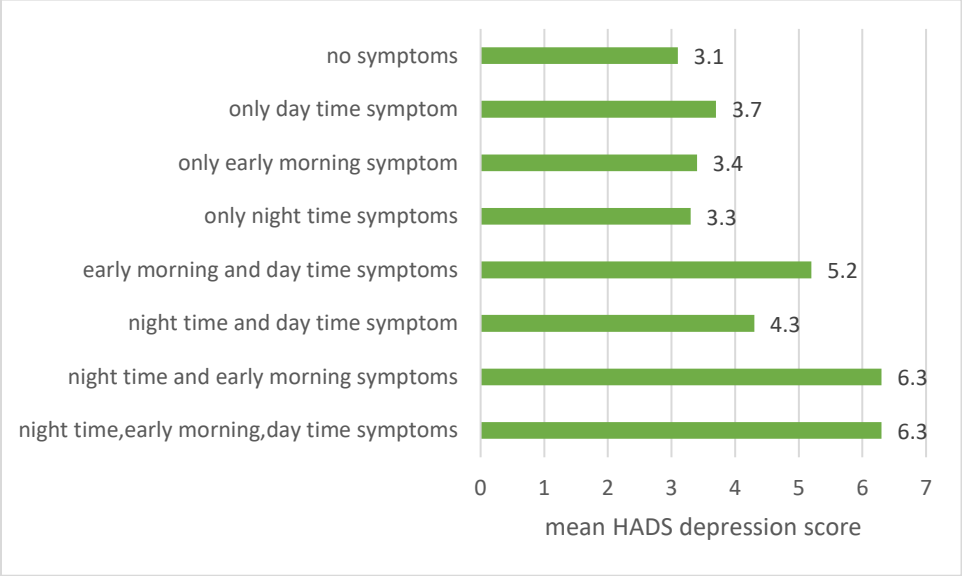
A)



B)


no symptoms
3.6
only day time symptom
3.8
only early morning symptom
4.3
only night time symptoms
6
early morning and day time symptoms
5.5
night time and day time symptom
5.8
night time and early morning symptoms
4.9
night time,early morning,day time symptoms
7
0 1 2 3 4 5 6 7 8
Mean HADS anxietyScore

C)


no symptoms
3.1
only day time symptom
3.7
only early morning symptom
3.4
only night time symptoms
3.3
early morning and day time symptoms
5.2
night time and day time symptom
4.3
night time and early morning symptoms
6.3
night time,early morning,day time symptoms
6.3
0 1 2 3 4 5 6 7
mean HADS depression score

D)

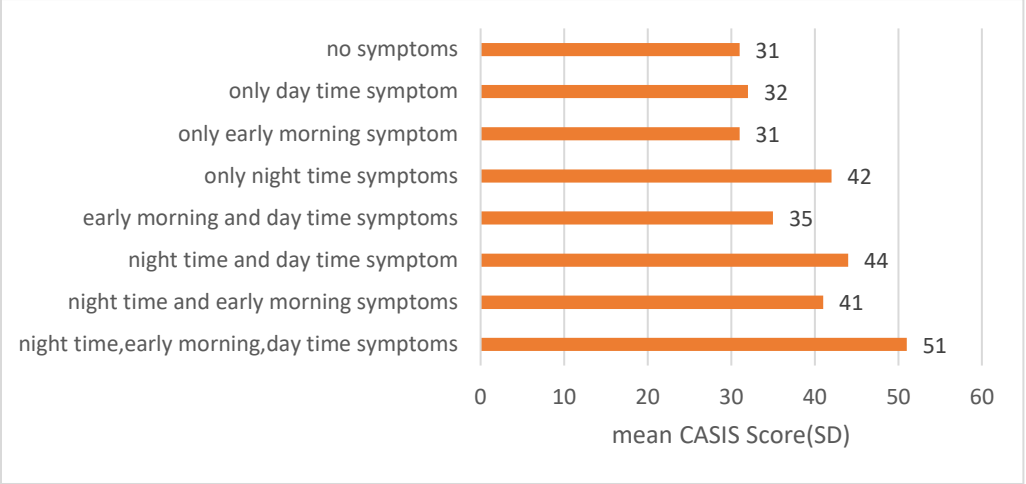


Fig.5 (A) Health status, (B) anxiety, (C) depression and (D) sleep quality according to each combination of 24-hour COPD symptoms. n = patients with available data for each outcome. CASIS, COPD and Asthma Sleep Impact Scale; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation.

DISCUSSION

In this observational study, more than half of patients reported experiencing COPD symptoms throughout the whole 24-hour day, despite receiving ongoing treatment for their COPD and almost 80% of patients had symptoms during at least two parts of the 24-hour day. While early morning and daytime symptoms were most frequent, night-time symptoms were also very common and almost two-thirds of patients experienced at least one night-time symptom during the week before baseline. Importantly, any symptoms in the early morning, daytime or night-time were associated with worse outcomes across a range of patient-reported measures including more severe dyspnoea, higher anxiety and depression levels and worse health status and sleep quality.

The observation that a large majority of patients experienced symptoms during at least two parts of the 24-hour day is consistent with results from a recent real-world study in almost 1500 patients. The study by Roche et al. showed that most patients had symptoms during the daytime and night-time and only 34% of patients experienced COPD symptoms in isolation during one part of the 24-hour day [13]. However, in contrast to the results reported here, in the previous study daytime symptoms were by far the most prevalent (97% of patients) with just over one-third of patients reporting symptoms when getting up in the morning. This discrepancy may relate to the different definitions of morning symptoms used; the Roche et al. study defined morning symptoms as those present on waking and did not include those symptoms that persisted later in the morning [13].

There is no objective definition of `night-time symptoms' in patients with COPD, and it has been suggested that night-time symptoms may be under-reported by physicians or may not be reported by patients [26]. The results of our study are consistent with a previous study in 2807 patients, which demonstrated that approximately 70% of patients reported experiencing night-time symptoms [7]. Together these data suggest a high prevalence of night-time symptoms in patients with COPD. Lung function exhibits circadian variation with reduced airflow during the night-time period [27]. The amplitude of this circadian variation has been shown to be increased in patients with COPD [28],[29] and it may contribute to night-time symptoms [26],[28]. In a previous study, wheezing was the most troublesome symptom at night, followed by cough [10]. In the present study cough and bringing up

phlegm were the most prevalent night-time symptoms suggesting that, in addition to reduced airflow, other mechanisms may be involved in mediating night-time symptoms including mucus hypersecretion, reduced ciliary activity or increased cough sensitivity. Further investigation of these processes is required to better understand the pathophysiology underlying night-time COPD symptoms.

Early morning symptoms have been reported to be most problematic for patients with COPD and can significantly impact on daily activities [10]-[12] and working life [13]. Furthermore, in a previous study, a quarter of patients with COPD reported that night-time symptoms were most troublesome and night-time was the second most problematic time for patients with severe COPD [12]. However, despite patients frequently reporting night-time symptoms, the impact that symptoms at night has on daily activities, such as getting up for work, is often under-estimated by physicians [7]. Previous studies have shown a significant association between night-time symptoms and the severity of airflow obstruction in patients with COPD [7],[14]. Interestingly, our results show that whilst there was a significant relationship between early morning and daytime symptoms and the severity of airflow limitation, this association was not significant for night-time symptoms and the prevalence of night-time symptoms was comparable across all severities of airflow limitation. Furthermore, symptoms in each part of the 24-hour day were inter-related, an observation that was consistent irrespective of COPD severity. These data suggest that the presence of night-time symptoms is not merely a consequence of more severe airflow limitation. Other mechanisms, such as decreased mucociliary clearance, could be involved. However, this study did not differentiate between different phenotypes of patients with COPD and further studies are required to determine if night-time symptoms are associated with a specific phenotype.

In each part of the 24-hour day, symptoms were associated with worse dyspnoea, health status, higher anxiety and depression levels, and greater sleep impairment. These are all outcomes that can impact on patients' daily living and overall well-being. The difference in CAT scores between patients with and without symptoms in each period exceeded the estimated minimal clinically important difference (2 points) recently proposed [30], suggesting that symptoms in any part of the 24-hour day may be associated with a clinically meaningful worsening of health status. Moreover, anxiety and depression levels were also significantly higher in patients with symptoms compared with patients without symptoms. In general, anxiety levels tended to be highest in patients who had any combination of night-time symptoms and depression levels were highest in patients with any combination of night-time/early morning symptoms. Depression is a common comorbidity in patients with COPD [2] and patients with severe COPD have a 2.5-fold higher risk of depression compared with matched controls [31]. Comorbid depression is associated with an increased risk of exacerbation and mortality in patients with COPD [32]. Since symptoms of depression tend to be worse in the morning we cannot rule out that higher levels of depression contribute to night-time and morning COPD symptoms. Of note, examining questions on COPD symptoms and the HADS questionnaire does not reveal common items, making confounding by wording unlikely. Finally, a similar pattern in the magnitude of HADS scores and symptom combinations was observed in patients with no medical history of anxiety or depression. Sleep was also significantly impaired in patients with symptoms in any part of the 24-hour day compared with patients without symptoms. As expected, the greatest impairment was observed in patients with night-time symptoms. Poor sleep quality or sleep disturbance in patients with COPD has been shown to be associated with worse health status, more exacerbations, increased healthcare resource utilisation and increased mortality [7],[33]. In this study, we also observed a significant relationship between symptoms in any part of the 24-hour day and physical activity levels: patients who were sedentary had more symptoms in each period than patients who were even moderately active. This may be important as low physical activity levels are significantly associated with poor quality of life and increased incidence of

depression in patients with COPD [34] and have been shown to be a strong predictor of mortality in patients with COPD [35],[36], and improving physical activity is an important goal in the treatment of COPD [9].

Overall, our results support previous studies showing that symptoms during the morning and the night-time are independently associated with worse outcomes in patients with COPD [7],[13]. COPD symptoms when getting up in the morning have been shown to be independently associated with worse health status and more exacerbations, and have a negative impact on daily activities [13]. Similarly, patients with night-time symptoms had significantly worse breathlessness and health status and were more likely to have morning symptoms than patients without night-time symptoms, even when these analyses were controlled for confounding factors such as disease severity [7]. Our results extend these studies by demonstrating that there is an inter-relationship between symptoms in each part of the 24-hour day and that symptoms in any part of the day are associated with worse patient-reported outcomes.

While these results demonstrate significant relationships between symptoms in each part of the 24-hour day and various aspects of patients' well-being, the analyses do not take into account confounding factors such as disease severity or comorbid conditions, which may also impact on patient-reported outcomes. Furthermore, no causal relationship can be inferred from the analyses as this was an observational study. Further investigation of the specific relationship between symptoms in each part of the 24-hour day and each outcome is required to establish whether symptoms are independently associated with the outcome, irrespective of underlying disease. While this study enrolled patients with mild to very severe COPD, only patients being treated in clinical practice (both primary care and specialist centres) were assessed. As such, the relevance of these observations for the wider population of patients with COPD, including those with undiagnosed COPD, requires further consideration.

CONCULSION

The results of this study demonstrate that despite receiving treatment for COPD, more than half of patients continued to have symptoms throughout the whole 24-hour day, including during the night-time and early morning periods. The relationship between night-time, early morning and daytime symptoms was observed irrespective of the severity of airflow obstruction. Patients with symptoms during any part of the 24-hour day also had significantly worse outcomes across a range of measures that impact on daily living, including health status, anxiety and depression levels and sleep quality compared with patients without symptoms. This suggests that current approaches to managing COPD may not adequately control symptoms, which can impact on a patient's overall well-being. Newer therapies, including long-acting bronchodilators that are administered twice-daily or ultra-long-acting bronchodilators, may be useful in improving symptom control during the night-time, whereas those with a rapid onset of action may have advantages in controlling early morning symptoms. It is important for physicians to manage patients' symptoms throughout the 24-hour day, even in those with mild airflow obstruction.

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