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Expert Review of Respiratory Medicine

ISSN: 1747-6348 (Print) 1747-6356 (Online) Journal homepage: https://www.tandfonline.com/loi/ierx20

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To cite this article: Amanda R. van Buul, Marise J. Kasteleyn, Niels H. Chavannes & Christian Taube (2017) Morning symptoms in COPD: a treatable yet often overlooked factor, Expert Review of Respiratory Medicine, 11:4, 311-322, DOI: 10.1080/17476348.2017.1305894

To link to this article: https://doi.org/10.1080/17476348.2017.1305894

Accepted author version posted online: 10 Mar 2017.
Published online: 22 Mar 2017.

EXPERT REVIEW OF RESPIRATORY MEDICINE, 2017
VOL. 11, NO. 4, 311–322
http://dx.doi.org/10.1080/17476348.2017.1305894

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REVIEW

Morning symptoms in COPD: a treatable yet often overlooked factor

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) patients experience the morning as the worst period of the day. Nevertheless, morning symptoms are not mentioned in COPD guidelines.
Areas covered: Different topics on morning symptoms are covered in this review to underline their importance: occurrence, tools for assessment and therapies to limit morning symptoms.
Expert commentary: Morning symptoms are common and have a negative influence on a patient's life. Pharmacotherapy seems to be effective in decreasing morning symptoms. A validated tool to assess morning symptoms is lacking. Therefore, more research should focus on assessing morning symptoms with a validated tool to further prove the effect of (pharmaco-) therapy. This will hopefully result in inclusion of morning symptoms in future guidelines.

ARTICLE HISTORY
Received 24 October 2016
Accepted 9 March 2017

KEYWORDS
COPD; impact; morning symptoms; pharmacotherapy; questionnaires; review; symptoms; tools

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common lung disease worldwide [1]. This chronic lung disease is characterized by chronic inflammation of the airways that result in irreversible and progressive airflow limitation [2]. COPD has great impact on a patient's life and is associated with a lower quality of life [3], lower physical activity [4], disabilities [5], and mortality [6]. Most common symptoms in COPD are dyspnea, cough, sputum production, wheezing, and chest tightness [7]. In the newest Global Initiative for Chronic Obstructive Lung Disease (GOLD) statements, symptoms also have a place in the gradation of the severity of COPD [7].

COPD symptoms differ day-by-day and symptoms may occur during any part of the day [8,9]. In recent years, it has become more clear that COPD patients experience the morning as the worst period of the day [10]. However, exact prevalence rates are unknown. Prevalence rates shown in current literature are derived from different questionnaires since a validated morning symptom questionnaire is lacking. Moreover, no consistent definition for the morning is used. Morning symptoms are not mentioned in international COPD guidelines and statements yet [7]. In contrast, asthma guidelines recommend physicians to ask asthma patients about morning symptoms [11]. Moreover, one statement recommends using morning symptoms as a tool to differentiate between asthma and COPD, where the presence of morning symptoms is an indicator for asthma [7]. Consequently, physicians do not routinely discuss morning symptoms with their COPD patients; morning symptoms are not usually targeted as a goal for therapy. Furthermore, in (medication) studies, researchers barely focus on morning symptoms and head-to-head comparisons between treatment options are scarce. Nevertheless, patients reported a need for discussing morning symptoms and they expect of prescribed medication that it will improve their ability to perform morning activities [12]. Therefore, there is need for more detailed assessment of morning symptoms not only in COPD in practice but also in research. Based on this statement, it is important to gather the current evidence of morning symptoms in COPD and underline this overlooked factor. The aim of this review is to critically assess the evidence of morning symptoms in COPD, with special focus on occurrence, the available morning symptom questionnaires, and current therapies. In the process of evaluating the current findings on this topic, gaps in our understanding and knowledge about morning symptom will become obvious. Defining these gaps can help to assess areas needing further research and could result in novel approaches to assess and treat mornings symptoms. This will probably lead to an inclusion of this topic in international guidelines in the future. This fits well into more modern approaches to use patient-reported outcomes in addition to traditional parameters as pulmonary function in the assessment of COPD patients.

2. Occurrence of morning symptoms and associated factors

It has been shown that the morning is the most troublesome period for COPD patients [3]. It is not well known why symptoms vary over the course of the day in COPD patients. Possibly, they suffer from morning symptoms since the morning is the most active part of the day including many activities of daily living such as washing and dressing. These activities can trigger morning symptoms [13]. Another suggestion is that it can be due to circadian variation in pulmonary function [14]. However, this change in pulmonary function does not directly translate into a difference in

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exercise capacity especially when assessing peak exercise capacity [15]. Interestingly, half of patients showed a diurnal change in peak exercise capacity independent of changes in pulmonary function [15]. The greatest exercise capacity was reached in the afternoon. In conclusion, the effects of circadian variation on morning symptoms are unclear and further research is warranted. At this moment, there is not a validated universal tool available to assess morning symptoms. Subsequently, in previous studies, the occurrence of morning symptoms was assessed with different tools. The studies showed that a substantial part of the COPD population suffer from morning symptoms with rates between 39.8% and 94.4% [12,16–24] (Figure 1). In some studies, the percentage of patients with morning symptoms is probably underestimated and in other studies probably overestimated. There are multiple factors that could influence the incidence rates. One possibility for differences between studies could be the usage of different definitions for the morning period. If the morning was defined as only the moment of waking up, patients who have problems with performing routine activities during the rest of the morning were missed, resulting in an underestimation of morning symptoms. A different reason could be that most of the time patients who were included in the studies were already being treated in clinical practices. These patients have probably already attended a health-care provider because of their symptoms and therefore, these studies might be biased toward more symptomatic patients. This bias would result in an overestimation of morning symptoms in the total COPD population. A third issue could be that patients underestimate their symptoms: 36% of patients who describe their symptoms as being mild to moderate are too breathless to leave the house [25], resulting in an underestimation of the burden of morning symptoms. Another reason could be that patients with severe morning symptoms are not willing to participate in studies that require visits to a study center. Since the patients with morning symptoms are probably missed in the studies requiring a morning visit, the occurrence of morning symptoms is most likely underestimated in those studies. Lastly, in some studies, physicians scored the severity rate for the patients' symptoms. Since physicians do not pay considerable attention to morning symptoms, they will probably underestimate the occurrence of morning symptoms as well.

2.1. Symptoms in the morning

Several studies have described the prevalence of symptoms in the morning [3,8,12,13,16,17,19–23,26,27]. Most frequently occurring morning symptoms in all COPD patients were coughing, shortness of breath, wheezing, and sputum production [16,19,20,22,27] (Figure 2). In two studies, one that used a 'physician completed patient record form' to assess morning symptoms and one that did 'symptom collection,' the percentages for cough, wheezing, and sputum were lower than in the previous mentioned studies [21,28]. The symptom chest tightness was common as well [16,20–22]. This symptom is more predominant in the morning compared with other parts of the day [17].

In patients who experience morning symptoms, the most common morning symptoms were coughing, shortness of breath, and sputum production [3,12,13,23] (Figure 3). Wheezing and chest tightness were common as well [17,23] but were not examined in every study. In a study that included only patients who experienced COPD symptoms affecting typical morning routines, patients suffered from wheezing (69%), chest tightness (63%), headache (35%), and exhaustion/tiredness (at least 23%) [13]. In symptomatic patients, 37% experienced the morning the as worst time of the day. The night is for symptomatic patients, the second worst part of the day [3]. Symptomatic patients suffer mostly from cough, dyspnea, and sputum production in the morning as opposed to other parts of the day [8,17,26] (Figure 4).

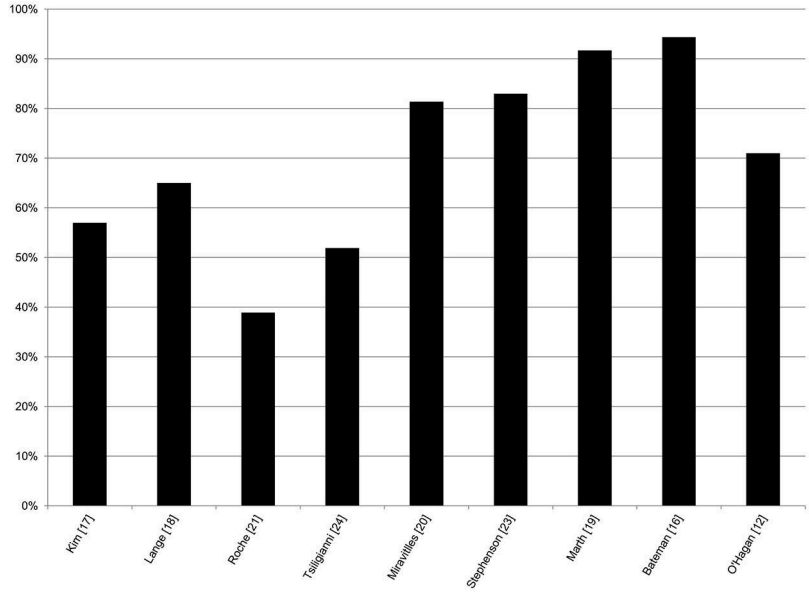

Figure 1. Occurrence of morning symptoms in all COPD patients in different clinical studies.
COPD: chronic obstructive pulmonary disease

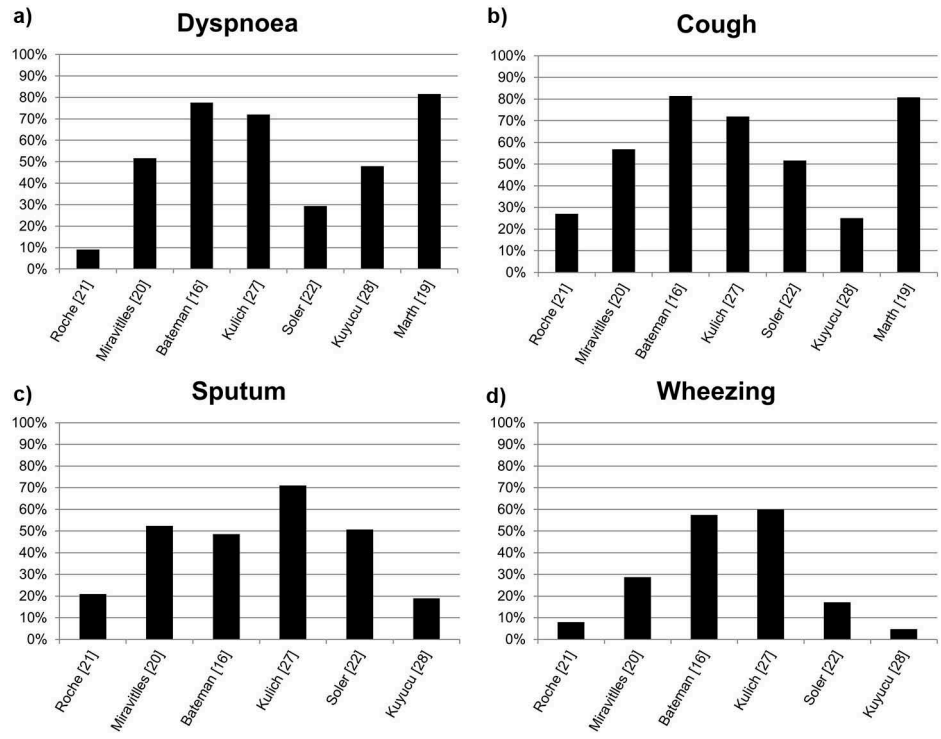

Figure 2. Occurrence of different types of morning symptoms in COPD patients in different studies.
a) Percentage of all patients that suffer from dyspnoea in the morning. b) Percentage of all patients that suffer from cough in the morning. c) Percentage of all patients that suffer from sputum production in the morning. d) Percentage of all patients that suffer from wheezing in the morning. COPD: Chronic obstructive pulmonary disease.

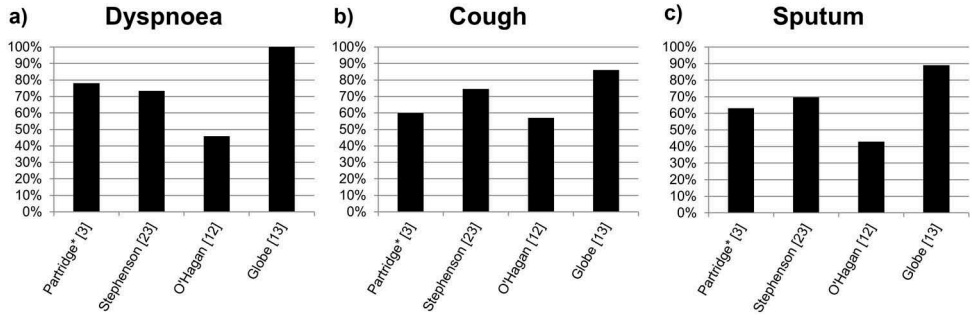

Figure 3. Occurrence of different types of morning symptoms in patients COPD with morning symptoms in different clinical studies.
a) Percentage of patients with morning symptoms that suffer from dyspnoea in the morning. b) Percentage of patients with morning symptoms that suffer from cough in the morning. c) Percentage of patients with morning symptoms that suffer from sputum production in the morning. *Severe group. "Severe" was defined in this study as: regular use of COPD medication plus a third level of breathlessness or above using Medical Research Council dyspnoea scale and one or more exacerbations in the preceding 12 months. COPD: chronic obstructive pulmonary disease.

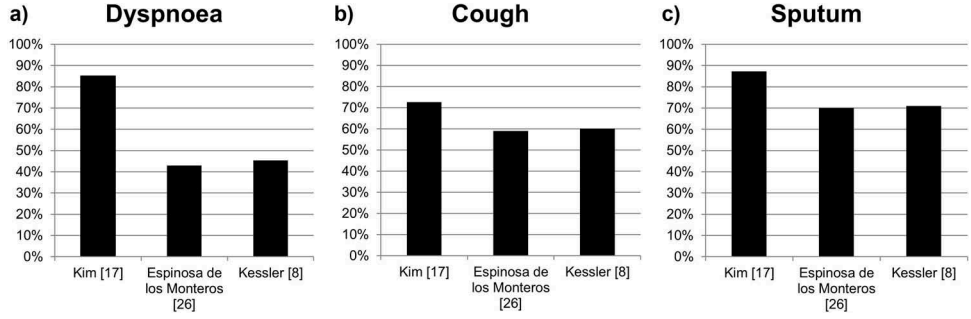

Figure 4. Occurrence of different types of morning symptoms in symptomatic COPD patients in different clinical studies.
a) Occurrence of dyspnoea in symptomatic COPD patients that mentioned the morning as most troublesome period of the day. b) Occurrence of cough in symptomatic COPD patients that mentioned the morning as most troublesome period of the day. c) Occurrence of sputum production in symptomatic COPD patients that mentioned the morning as most troublesome period of the day. COPD: chronic obstructive pulmonary disease

2.2. Factors associated with morning symptoms

Multiple factors are associated with morning symptoms. These factors include physical activity [29], nighttime symptoms [20,23,24], poorer health status [21–24], current smoking [3,21,23,24], an exacerbation in the previous 12 months [21,24,30], more depression, and anxiety [20–23]. Furthermore, morning symptoms are associated with worsening of symptoms (that do not require a visit to a health-care provider) [21] and more use of rescue medication [21,23,24]. But also, more primary care visits are associated with morning symptoms [30]. The effects of modifying these factors on morning symptoms have not been studied yet.

2.3. Conclusion

In conclusion, most COPD patients suffer from morning symptoms. The most common symptoms in the morning are dyspnea, cough, sputum, and wheezing. To get more insight in the occurrence of morning symptoms, there is a need for a clear definition of the morning. The pathophysiology of variation of symptoms of the day is unknown.

3. Tools to assess morning symptoms

In the recent years, morning symptoms in COPD have become of more interest in research. The choice of the questionnaire has a major influence on detected prevalence and severity scores of morning symptoms. A validated morning symptoms questionnaire is lacking; so, different tools and questionnaires have been utilized. This chapter summarizes the used morning symptom questionnaires. An overview is shown in Table 1. Outcomes of the different questionnaires are reported in Table 2.

3.1. Specific morning symptom questionnaires

In 2010, the 'Capacity of Daily Living during the Morning (CDLM)' was developed [38]. This questionnaire was the first morning symptom questionnaires. In the CDLM, patients report their ability to carry out six different morning activities, including washing themselves, drying themselves, dressing in the morning, eating breakfast, and walking around the house early and later in the morning. Patients are able to rank their ability to carry out these morning activities from 'not at all difficult' to 'extremely difficult.' The CDLM should be filled out after completing all morning activities. The estimated minimally important difference is 0.20. This questionnaire shows a good-to-high reliability. Other tools that have been used to assess morning symptoms in particular were the morning assessment of the COPD eDiary [27], the 'Patient-reported outcome (PRO) Morning COPD symptoms Questionnaire' [34], the 'Manchester Early Morning, Symptoms Index (MEMSI)' [39], the 'Early-Morning Symptoms of COPD Instrument (EMSCI)' [40], the 'Morning Activity Questionnaire (MAQ)' [17], and the 'chronic obstructive pulmonary disease morning symptom diary' (COPD-MSD) [13]. The morning assessment of the COPD eDiary is a questionnaire that contains five morning symptom items ('shortness of breath,' 'phlegm/mucus,' 'chest tightness,' 'wheezing,' and 'coughing') and two impact items ('bothered by COPD' and 'difficulty with activities'). Patients are able to rate all items from 'none' to 'worst possible.' The questionnaire must be completed between waking up and before inhalation of medication. A very high internal consistency for all seven diary items is found. The PRO-Morning COPD symptoms Questionnaire is a six-item questionnaire that was derived from the morning assessment of the COPD eDiary. The MEMSI is a simple 10-item one-dimensional questionnaire. During development, COPD patients agreed that the five-option Likert-type scale ('never' to 'always') was relevant and easy to understand. This tool shows a good test reliability, test–retest repeatability, and validity, but the minimal clinically important difference has not been determined yet. The EMSCI assesses morning symptoms ('yes' or 'no'), the severity of these symptoms ('mild' to 'very severe'), and the impact of these symptoms ('mild' to 'very severe'). Patients should complete the questionnaire between 7 AM and 11 AM. This tool is still under validation. The MAQ consists of one question about the impact of morning symptoms on morning activities in general. Patients are able to score the impact from 'minimal' to 'maximal.' The most recently developed questionnaire is the COPD-MSD [13]. For the development of this questionnaire, COPD patients were interviewed about their symptoms in the morning. The phrases used in the questionnaire contain words that were used by patients in the interviews, resulting in a questionnaire that is understandable for patients. The COPD–MSD is still under development, because it still contains too many items and this tool has not been validated yet.

3.2. Questionnaires that included morning symptoms

There are also questionnaires that include morning symptoms or can be used as morning symptom questionnaires because they are suitable for each part of the day. The Global Chest Symptoms Questionnaire (GCSQ) is a two-item questionnaire developed to measure shortness of breath and chest symptoms at any part of the day (including the morning) [38]. Patients are able to rank their shortness of breath and chest symptoms from 'no symptoms at all' to 'extreme symptoms.' This questionnaire shows a good-to-high reliability. Other questionnaires that include morning symptom questions are the 'Night-time, Morning and Daytime Symptoms of COPD questionnaire' [20], the 'Nighttime Symptoms Questionnaire' [33], the 'Clinical Symptom Questionnaire (CSQ)' [17], and the St. George's Respiratory Questionnaire [41]. The 'Night-time, Morning and Daytime Symptoms of COPD questionnaire' is a 33-item questionnaire about the prevalence, frequency, and severity of COPD symptoms. Ten out of 33 questions are about morning symptoms. Patients are asked about the frequency of breathlessness, coughing, bringing up phlegm or mucus, chest tightness, chest congestion, and wheezing during the period from getting out of bed until 11 AM. Patients are able to rate the severity of symptoms from 'no symptoms' to 'very severe symptoms.' The questionnaire was linguistically validated. The 'Nighttime Symptoms Questionnaire' is an 11-item questionnaire that contains two questions about severity and impact of

Table 1. Tools to measure morning symptoms.

Tool	Number of items	Range	Topics			Validated yes/no	Notable aspects of tool
			Sympt	Severity	Impact		
ACQ	1	0–6	X	X		Not for COPD	Validated ACQ
'A patient record form'	NA	1–7	X	X	X	No	Symptoms were reported in detail by the physician
'A 30-min survey with questions about COPD symptoms'	NA	NA	X	X	X	No	Not a specific morning symptom questionnaire
Patients were asked to evaluated the severity of morning symptoms	NA	0–4	X	X	X	No	Different kind of symptoms was separately assessed and also separately reported
CSQ and MAQ	4 and 1	1–10	X	X	X	No	If the CSQ was positive for morning symptoms, the MAQ was filled out too
'Questionnaire according to coughing/breathlessness during the morning/night'	5	0–5	X	X		No	5-Item questionnaire that contained two questions about symptoms in the morning
Morning assessment of the COPD eDiary	18	0–10	X	X	X	No	Five symptoms and two impact items were assessed
'A 20-min questionnaire'	31	Impact: 1–3	X		X	No	The questionnaire was based on a review of previous published research on most common symptoms in COPD
COPD-MSD	19	SOB: 0–6. All other items: 0–5. Total: 0–96	X	X	X	No	Next step is reducing length of the tool and validation
Nighttime Symptoms Questionnaire	11	0–4	X	X	X	No	11-Item questionnaire that included 2 questions about morning symptoms
PRO-morning COPD Symptoms Questionnaire	2x6	0–60	X	X	X	No	6 Questions at home, at the time of waking up, pre-morning medication; 6 questions 3 h after morning medication
GCSQ and CDLM	1 and 8	GCSQ: 0–4 CDLM: 0–5	X	X	X	No	Questionnaires were filled out at home
'20-min interview COPD symptoms'	NA	NA	X		X	No	Symptomatic patients were asked what moment of the day was most bothersome
COPD symptoms questionnaire	NA	1–5 (only for individual morning symptoms 0–4)	X	X	X	No	Questionnaire developed by the sponsor
'20–30 min questionnaire'	NA	NA	X		X	No	A feasibility study was performed prior to patient recruitment
'A 34-item questionnaire'	34	NA	X		X	No	There were pilot interviews before the use of this questionnaire
'Symptom collection'	NA	Impact: 1–10	X		X	No	Symptoms were obtained in a single visit
EMSCI	14	0–4	X	X	X	No	Was completed every day between 7 AM and 11 AM
Night-time, morning and daytime symptoms of COPD questionnaire	33	1–5	X	X	X	No	33-Item questionnaire that included 10 items about morning symptoms

ACQ: Asthma control questionnaire; CDLM: Capacity of Daily Living during the Morning questionnaire; COPD: chronic obstructive pulmonary disease; COPD-MSD: chronic obstructive pulmonary disease morning symptom diary; CSQ: Clinical Symptom Questionnaire; EMSCI: Early-Morning Symptoms of COPD Instrument; GCSQ: Global Chest Symptoms Questionnaire; MAQ: Morning Activity Questionnaire; PRO: patient-reported outcome; SOB: shortness of breath; Sympt: Symptoms.

Table 2. Outcomes of morning symptoms questionnaires.

Tool	Studies (authors)	Occurrence of morning symptoms	Mean score in the study (at baseline)
ACQ	Tsiligianni et al. [24]	51.9%	1.1
'A patient record form'	Roche et al. [21]	39.8%	Impact: 3.96
Night-time, Morning and Daytime Symptoms of COPD questionnaire	Miravitlles et al. [20]	81.4%	44.1% Mild (score 1); 43.8% moderate (score 2)
	Soler et al. [22] (Spanish subgroup of the ASSESS study [20])	71.3%	53.7% Mild (score 1); 40.2% moderate (score 2)
EMSCI	Singh et al. [31]	NA	NA
	D'Urzo et al. [32]	NA	ACLI/FORM 400/12 mcg: 1.19 (0.63); ACLI/FORM 400/6 mcg: 1.15 (0.64); ACLI 400 mcg: 1.13 (0.65); FORM 12 mcg: 1.13 (0.66); Placebo: 1.07 (0.58)
	Bateman et al. [16] (pooled data from AUGMENT study [32] and ACLIFORM study [31])	94.4%	1.2
'a 30-minute survey with questions about COPD symptoms'	Stephenson et al. [23]	83.0%	NA
Patients were asked to evaluated the severity of morning symptoms	Marth et al. [19]	91.7%	Proportion of patients with at least moderate symptoms: 57.7%
CSQ and MAQ	Kim et al. [17]	57.0%	NA
'Questionnaire according to coughing/breathlessness during the morning/night'	Lange et al. [18]	65.0%	NA
Morning assessment of the COPD eDiary	Kulich et al. [27]	NA	2.12–3.20
'A 20-min questionnaire'	O'Hagan et al. [12]	71.0%	Most impact on stairs (only 21% symptom free)
COPD-MSD	Globe et al. [13]	Inclusion criterion	NA
Nighttime Symptoms Questionnaire	Kerwin et al. [33]	NA	NA
PRO-morning COPD Symptoms Questionnaire	Marin et al. [34]	NA	16.6
GCSQ and CDLM	Welte et al. [35]	NA	NA
	Partridge et al. [36]	NA	NA
'20-min interview COPD symptoms'	Espinosa de los Monteros et al. [26]	NA	NA
COPD symptoms questionnaire	Beier et al. [37]	NA	ACLI: 2.36; TIO: 2.25
'20–30 minute questionnaire'	Kessler et al. [8]	NA	NA
'A 34-item questionnaire'	Partridge et al. [3]	NA	NA
'Symptom collection'	Kuyucu et al. [28]	NA	Most impact ongoing up/down stairs: 6.7 (2.6)

ACLI: aclidinium; ACQ: Asthma control questionnaire; CDLM: Capacity of Daily Living during the Morning questionnaire; COPD: chronic obstructive pulmonary disease; COPD-MSD: chronic obstructive pulmonary disease morning symptom diary; CSQ: Clinical Symptom Questionnaire; EMSCI: Early-Morning Symptoms of COPD Instrument; FORM: formoterol; GCSQ: Global Chest Symptoms Questionnaire; MAQ: Morning Activity Questionnaire; PRO: patient-reported outcome.

early morning symptoms. The patients should fill out this questionnaire each morning in an electronic diary. The CSQ is a self-reported questionnaire about clinical symptoms in each part of the day. Patients are able to report in which part of the day, their symptoms are most troublesome. They are able to choose between 'on waking,' 'in the morning,' 'in the afternoon,' 'in the evening,' or 'at night.' When patients experience the morning as the worst part of the day, they can also complete the MAQ. The MAQ was designed to give insight in the impact of morning symptoms on morning activities since not every patient with symptoms in the morning experiences an impact on morning activities.

One study reported an alternative way to identify severe morning symptoms in COPD patients [24]. They stated that the Clinical COPD Questionnaire (CCQ) [42] was also able to identify patients with morning symptoms since patients with severe morning symptoms had higher scores in CCQ and these patients were not really missed when only measuring the CCQ. One other study used the Asthma Control Questionnaire [43], a questionnaire that has been developed for asthma, to assess morning symptoms in COPD patients [24].

3.3. Conclusions of tools to assess morning symptoms

In conclusion, at this moment, there is no standardized validated questionnaire to assess morning symptoms that is regularly used in clinical research. However, several questionnaires have been developed and it is perceived that for each new study, a novel morning symptom questionnaire is utilized. Only the EMSCI and the GCSQ combined with the CDLM were used in more than one study.

4. Therapy to limit morning symptoms

4.1. Pharmacotherapy

The effect of pharmacotherapy on morning symptoms has been studied and is becoming of more interest in the recent years. One study described that 79% of patients believed that their medication provided sufficient relief of their morning symptoms [12]. Fourteen percent of patients with morning symptoms described that the use of any inhaled medication reduced the severity of shortness of breath during morning activities [13].

4.1.1. Bronchodilators

The basis of pharmacotherapy for COPD is bronchodilators [7]. However, the effect of long-acting beta2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) on morning symptoms has only been assessed in a few studies. In recent studies, frequent targets for treatment were the muscarinic receptors because of the diurnal cholinergic effects on pulmonary function. Most randomized controlled trials that studied the effect of a LAMA on morning symptoms studied the effect of aclidinium. Aclidinium twice daily reduced the proportion of patients with at least moderate morning symptoms [18,19,37]. Treatment with once-daily glycopyrronium [34] or tiotropium [34,37] resulted in a decrease in morning symptoms (Table 3).

So far, aclidinium has been most extensively studied in this context and treatment with aclidinium resulted not only in a decrease of all morning symptoms, but also in a significant improvement of the individual morning symptoms sputum production, shortness of breath, wheezing, coughing, and limitations of morning activities when compared with placebo. There was a quantitatively greater improvement when compared with tiotropium [37]. It could be speculated that the positive effect of aclidinium could be due to the twice-daily formula and the evening administration of the bronchodilator that could lead to better nighttime bronchodilation and potentially less symptoms in the morning. However, the effects of a once-daily formula in the evening on morning symptoms have not been adequately studied yet. In this context, it also needs to be considered that the onset of acting of different LAMAs could be a factor that may influence morning symptoms [44]. In two studies, formoterol was added to aclidinium in two different fixed-dose combination [31,32]. In both studies, combination therapy was more effective in improving 24-h symptom control compared with placebo [16], or the each component alone.

4.1.2. Bronchodilators combined with inhaled corticosteroids

In the treatment of COPD, the effectiveness of inhaled corticosteroids (ICS) is controversial, but certain phenotypes of COPD patients seem to benefit from ICS treatment [45]. The effect of budesonide/formoterol combined with tiotropium significantly improved morning symptoms predose as well as 5 and 15 min postdose as compared with tiotropium alone [35]. In one other study, budesonide/formoterol was compared with salmeterol/fluticasone [36]. This study showed no significant difference in morning symptoms, but treatment with budesonide/formoterol resulted in significant improvement in the ability to perform tasks in the morning.

4.1.3. Important issues in medication studies

The positive effects of pharmacotherapy on morning symptoms are encouraging. Obviously, 17.9–40.1% of patients with morning symptoms reported that they did not use inhaled medication at baseline [16,24]. It is unclear whether the medication was not prescribed or the patient did not use it. However, it is remarkable that symptomatic patients did not use medication. Previous research has shown that low treatment adherence was associated with morning symptoms [21,23], indicating that it is important to stimulate therapy adherence to prevent morning symptoms. In one study, low treatment adherence was defined as a score lower than six on the Morisky Medication Adherence Scale [23]. The Morisky Medication Adherence Scale [46] is a scale to assess adherence to medication; the lower the score, the less is adherence. One other study defined low treatment adherence as physician-reported low treatment adherence [21]. In addition, one study showed that most of the COPD patients do not adjust medication during a symptomatic period [8]. Patients take their medication too late in the morning [3]. It is important to instruct to

Table 3. Effects of inhaled medication on morning symptoms.

Author	Tool	Medication	Score on baseline	Effect size (p-value if available)
Kerwin et al. [33]	Nighttime Symptoms Questionnaire	ACLI 200 mcg[a] vs. ACLI 400 mcg[a] vs. placebo	NA	Severity of breathlessness ACLI 200 mcg −0.31 (0.77)[b] vs. placebo $p < 0.01$ ACLI 400 mcg −0.32 (0.79)[b] vs. placebo $p < 0.001$ Placebo −0.09 (0.61)[b] Impact of breathlessness: ACLI 200 mcg −0.22 (0.69)[b] vs. placebo $p < 0.01$ ACLI 400 mcg −0.28 (0.76)[b] vs. placebo $p < 0.001$ Placebo −0.03 (0.56)[b]
Marin et al. [34]	PRO-morning COPD Symptoms Questionnaire	GLY 50 mcg once-daily vs. TIO 18 mcg once-daily	GLY: 16.7 (11.1) TIO: 16.6 (10.0)	GLY: 1.9 (7.8) $p = 0.002$[b] TIO: 1.2 (7.9) $p = 0.063$[b]
Singh et al. [31]	EMSCI	ACLI/FORM 400/12 mcg[a] vs. ACLI/FORM 400/6 mcg[a] vs. ACLI 400 mcg[a] vs. FORM 12 mcg[a] vs. placebo	NA	ACLI/FORM 400/12 mcg −0.21 units (−17.7%)[b] ACLI/FORM 400/6 mcg −0.24 units (−20.2%)[b] ACLI 400 mcg −0.13 units (−10.2%)[b] FORM 12 mcg −0.17 units (−14.0%)[b] Placebo −0.12 units (−9.6%)[b] ACLI/FORM (both doses) vs. placebo $p < 0.05$ ACLI/FORM (both doses) vs. ACLI 400 mcg $p < 0.01$ ACLI/FORM 400/6 mcg vs. FOR 12 mcg $p < 0.05$
D'Urzo et al. [32]	EMSCI	ACLI/FORM 400/12 mcg[a] vs. ACLI/FORM 400/6 mcg[a] vs. ACLI 400 mcg[a] vs. FORM 12 mcg[a] vs. placebo	ACLI/FORM 400/12 mcg: 1.19 (0.63) ACLI/FORM 400/6 mcg: 1.15 (0.64) ACLI 400 mcg: 1.13 (0.65) FORM 12 mcg: 1.13 (0.66) Placebo: 1.07 (0.58)	ACLI/FORM 400/12 mcg −0.24 units (−20.3%)[b] ACLI/FORM 400/6 mcg −0.26 units (−22.3%)[b] ACLI 400 mcg −0.15 units (−12.9%)[b] FORM 12 mcg −0.18 units (−15.7%)[b] Placebo −0.11 units (−10.5%)[b] ACLI/FORM (both doses) vs. placebo $p < 0.01$ ACLI/FORM (both doses) vs. ACLI 400 mcg $p < 0.05$
Bateman et al. [16] (pooled data from AUGMENT study [32] and ACLIFORM study [31])	EMSCI	ACLI/FORM 400/12 mcg[a] vs. ACLI 400 mcg[a] vs. FORM 12 mcg[a] vs. placebo	ACLI/FOR 400/12 mcg 1.3 (0.7) ACLI 400 mcg 1.3 (0.7) FOR 12 mcg 1.2 (0.7) Placebo 1.2 (0.6)	ACLI/FORM 400/12 mcg −0.23 units (−17.0%)[b] ACLI 400 mcg −0.14 units (−10.7%)[b] FORM 12 mcg −0.17 units (−13.6%)[b] ACLI/FORM 400/12 mcg vs. ACLI 400 mcg $p < 0.001$ ACLI/FORM 400/12 mcg vs. FOR 12 mcg $p < 0.01$
Welte et al. [35]	GSCQ and CDLM	TIO 18 mcg once-daily plus placebo vs. TIO 18 mcg once-daily plus BUD/FORM 320/9 mcg[a]	NA	GSCQ predose breathlessness: TIO + placebo: −0.036[b]; TIO + BUD/FORM: −0.184[b]; TIO + BUD/FORM vs. TIO + placebo: −0.148 $p = 0.001$ GSCQ predose chest tightness: TIO + placebo: −0.029[b]; TIO + BUD/FORM: −0.119[b]; TIO + BUD/FORM vs. TIO + placebo: −0.090 $p = 0.051$ GSCQ 15 min postdose breathlessness: TIO + placebo: −0.310[b]; TIO + BUD/FORM: −0.495[b]; TIO + BUD/FORM vs. TIO + placebo: −0.185 $p < 0.001$ GSCQ 15 min postdose chest tightness: TIO + placebo: −0.231[b]; TIO + BUD/FORM: −0.352[b]; TIO + BUD/FORM vs. TIO + placebo: −0.121 $p = 0.014$ CDLM: TIO + placebo: 0.083[b]; TIO + BUD/FORM: 0.264[b]; TIO + BUD/FORM vs. TIO + placebo: 0.180 $p < 0.014$
Partridge et al. [36]	GSCQ and CDLM	BUD/FORM 320/9 mcg[a] vs. SAL/FLU 50/500 mcg[a]	NA	CDLM BUD/FORM: −0.22[b] SAL/FLU: −0.12[b] BUD/FORM vs SAL/FLU: mean difference 0.10 ($p < 0.05$)
Marth et al. [19]	Patients were asked to evaluated the severity of morning symptoms	Newly initiated on treatment with ACLI 400 mcg twice-daily as first-line or add-on	Proportion of patients with at least moderate symptoms: 57.7%	$p < 0.0001$[b]

(*Continued*)

Table 3. (Continued).

Author	Tool	Medication	Score on baseline	Effect size (p-value if available)
Kim et al. [17]	CSQ and MAQ	'Treated according to routine clinical practices based on the GOLD guidelines'	Getting out of bed: 5.2 (2.6) Using the toilet: 4.3 (2.6) Washing yourself: 5.7 (2.4) Drying yourself: 4.3 (2.6) Dressing yourself: 3.7 (2.4) Preparing breakfast: 2.7 (2.3) Eating breakfast: 2.8 (2.2)	Getting out of bed: −1.2 (1.4) $p < 0.0001$[b] Using the toilet: −0.8 (1.7) $p = 0.0001$[b] Washing yourself: −1.9 (2.0) $p < 0.0001$[b] Drying yourself: −1.2 (1.6) $p < 0.0001$[b] Dressing yourself: −1.1 (1.6) $p < 0.0001$[b] Preparing breakfast: −0.7 (1.2) $p = 0.0021$[b] Eating breakfast: −1 (1.5) $p < 0.0001$[b]
Lange et al. [18]	Questionnaire according to: coughing/ breathlessness during the morning/ night and sleep quality	ACLI 322 mcg[a] (initial therapy, change of treatment, or add-on therapy)	Proportion of patients with morning symptoms: 65% Moderate to very severe: 40%	Severity of morning symptoms: −0.60 (2.51)[b] $p < 0.001$
O'Hagan et al. [12]	'A 20-min questionnaire'	'Their medication'	NA	79% of patients believed that their medication provided sufficient relief in morning symptoms
Globe et al. [13]	NA	Rescue inhaler or nebulizer	NA	14% of patients described reduction of the severity of shortness of breath
Beier et al. [37]	COPD symptoms questionnaire (developed by the sponsor)	ACLI 322 mcg[a] vs. TIO 18 mcg once-daily vs. placebo	ACLI 2.36 TIO 2.25	ACLI −0.22 vs. placebo $p < 0.001$ TIO −0.12 vs. placebo $p < 0.05$

ACLI: Aclidinium; BUD: budesonide; CDLM: Capacity of Daily Living during the Morning questionnaire; COPD: chronic obstructive pulmonary disease; CSQ: Clinical Symptom Questionnaire; EMSCI: Early-Morning Symptoms of COPD Instrument; FLU: Fluticasone; FORM: formoterol; GCSQ: Global Chest Symptoms Questionnaire; GLY: glycopyrronium; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MAQ: Morning Activity Questionnaire; PRO: patient-reported outcome; SAL: salmeterol; TIO: tiotropium.

[a]twice-daily.

[b]vs. baseline.

patients how and when they should use their medication as this may reduce morning symptoms.

Notably, none of the interventional studies used morning symptoms as primary end point but used pulmonary function as primary end point. In these studies, pulmonary function tests were performed before or just after the inhalation of the morning dose. This resulted in the inclusion of more patients with milder morning symptoms since patients with severe morning symptoms will not be able to come to the study center in the morning to perform a tough pulmonary function test. This may have resulted in a smaller measured treatment effect since the included patients already have less morning symptoms.

4.2. Non-pharmacological therapy

Patients with morning symptoms were more likely to have used oxygen in the past week than patients without morning symptoms [23].To our knowledge, there are no studies performed that evaluated the effect of conventional therapies, such as physiotherapy, exercise training, cough therapy, energy conservation techniques, nutrition, breathing techniques, relaxing techniques, education and self-management, integrated care programs, maintaining regular contact with health-care providers, smoking cessation, social support, cognitive therapy, and pulmonary rehabilitation on morning symptoms. Although these therapies are well accepted in the treatment of COPD patients [7], the effects on morning symptoms are unknown.

4.3. Conclusion of therapy to limit morning symptoms

Pharmacotherapy has shown positive effects on morning symptoms. Most intervention studies on morning symptoms studied the effect of aclidinium. Hence, treatment with any LAMA resulted in less morning symptoms [17,24]. However, in all studies, morning symptoms were assessed with non-validated questionnaires. Medication adherence is important too and low medication adherence is associated with morning symptoms. For physicians, it is important to discuss medication adherence, the time of use of the inhaled medication and inhalation technique should be checked.

5. Conclusion

Morning symptoms occur in the majority of COPD patients. However, exact prevalence rates are unknown because a clear definition of morning symptoms and a validated morning symptom questionnaire are lacking. Despite the high frequency of morning symptoms, there is barely attention for it and this important topic is absent in current guidelines. Pharmacotherapy seems to improve morning symptoms with also significant effects on the ability to perform morning activities. It seems to be important to control morning symptoms so as to provide a better start of the day. There seems to be an important role for medication adherence and time of medication use.

6. Expert commentary

In the past decade, morning symptoms in COPD have become a focus in research. The amount of publications about morning symptoms and COPD is increasing. This is an important evolution, because the prevalence of morning symptoms is a substantial problem in COPD patients. We think that symptoms are becoming of more interest, because dyspnea is one of the items in a simple multidimensional grading system to predict the risk of death [47] and it is already implemented in the GOLD classification [7]. Still, future research should give us more information about the physiology and the impact of morning symptoms on other well-respected outcomes such as mortality and hospitalizations.

At this moment, a validated tool to assess morning symptoms is lacking. To study morning symptoms, a validated tool is needed. We recommend a tool that includes symptoms, severity of symptoms, and impact of the symptoms on activities. Also, a clear definition of the morning should be added. It would also be useful to compare morning symptom questionnaires to identify which one covers morning symptoms the best and which one is most patient friendly. This will result in a standardized evaluation of morning symptoms, especially in prospective studies with morning symptoms as primary end point. In this way, we will be able to better understand why morning symptoms occur, the impact of morning symptoms and the underlying physiology. This can also result in new targets for therapy.

Up till now, there is evidence that pharmacotherapy significantly improves morning symptoms. However, some patients are still uncontrolled despite using inhaled medication; so, further research is needed to fine-tune therapy. From our view, future research should focus on medication in a once-daily formula that is provided in the evening. This will support the suggestions that an evening dose inhibits sputum production during the night. Thereby, it should be evaluated whether or not it will be better to prescribe patients with morning symptoms a combination of LABA/LAMA and ICS. Probably, patients with morning symptoms will profit more from this combination because patients with morning symptoms have more frequent exacerbations. Recently, a review concluded that some phenotypes with frequent exacerbations require an ICS [48] and therefore, it could be possible that also the morning symptom phenotype will profit from ICS therapy. However, this hypothesis is so far not based on clinical data and needs to be further studied. The development of fast-acting inhaled medication has been a positive step in limiting morning symptoms too. The effect of fast-acting medication could result in a faster start up in the morning but more research is warranted to show the effectiveness of this approach. Thereby, physicians should keep in mind that they don't only prescribe the medication, but also make an indication of compliance. Physicians should stimulate and evaluate adherence to therapy. Therapy adherence can be increased by raising awareness with the patient of the disease and by improving care cooperation [49] between different health-care providers and patients [50]. To evaluate adherence, questionnaires can be filled out in the waiting room. Moreover, e-health is upcoming in COPD and this will probably be a tool

to increase awareness of the disease and may be a helpful tool in detecting nonadherence.

Beside pharmacotherapy, we also expect that in further research, different treatment approaches will be combined, because in our opinion, pharmacotherapy alone will not solve morning symptoms in all patients. For example, personalized treatment with inhaled medication combined with cough instructions, exercise, breathing and relaxing techniques, self-management, nutrition, oxygen therapy, cognitive behavior therapy, smoking cessation, and/or pulmonary rehabilitation. For future studies, it is also important to include study visits in the afternoon. In most of the present studies, it is not clear in which part of the day, the pulmonary function tests were performed (most of the time during 'general care,' so this can be any part of a working day). In studies about morning symptoms, this is important because patients with severe morning symptoms will not decide to participate in a morning symptoms study because they are not able to come in the morning. In future studies assessing morning symptoms as primary end point, we suggest that patients fill out questionnaires in the morning at home and the time of the study visit could be in the afternoon.

7. Five-year view

In conclusion, morning symptoms in COPD are an important topic. However, the underlying pathophysiology is not yet well understood. We expect that in 5 years due to further research, the underlying pathophysiology and risk factors for morning symptoms will become more clear. We expect that within 5 years, there will be a validated morning symptom questionnaire and more studies will have been done to investigate the effect of pharmacotherapy, for example combinations of (fast-acting) inhaled medication at different times of the day. We also expect that the effect of non-pharmacological interventions will be studied in morning symptoms. This will result in evidence-based treatment plans to limit morning symptoms. Including these plans in guidelines fit well in the upcoming trend for personalized medicine. We strongly believe that morning symptoms should be included in guidelines and statements because we cannot ignore such an important topic in COPD.

Key issues

- 39.9 to 94.4% of COPD patients are suffering from morning symptoms.
- Most mentioned morning symptoms are dyspnoea, cough and sputum production.
- Morning symptoms are not mentioned in COPD guidelines yet.
- There is no validated morning symptoms questionnaire available yet. Such a questionnaire is needed to perform structured future research.
- Morning symptoms seems to be a target for therapy.
- Pharmacotherapy can help to decrease morning symptoms in COPD patients.
- Most intervention studies on morning symptoms studied the effect of long-acting muscarinic antagonists.
- We strongly believe that morning symptoms should be included into guidelines and statements.

Acknowledgement

We thank Steven J.H.A. McDowell for critical reading the manuscript.

Funding

Leiden University Medical Center.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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