Systematic literature review of patient-reported outcome measures used in assessment and measurement of sleep disorders in chronic obstructive pulmonary disease

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Background: Sleep problems are common in patients with chronic obstructive pulmonary disease (COPD), but the validity of patient-reported outcome measures (PROMs) that measure sleep dysfunction has not been evaluated. We have reviewed the literature to identify disease-specific and non-disease-specific sleep PROMs that have been validated for use in COPD patients. The review also examined the psychometric properties of identified sleep outcome measures and extracted point and variability estimates of sleep instruments used in COPD studies.

Methods: The online EMBASE, MEDLINE, PsycINFO, and SCOPUS databases for all years to May 2014 were used to source articles for the review. The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Criteria from the Medical Outcomes Trust Scientific Advisory Committee guidelines were used to evaluate the psychometric properties of all sleep PROMs identified.

Results: One COPD-specific and six non-COPD-specific sleep outcome measures were identified and 44 papers met the review selection criteria. We only identified one instrument, the COPD and Asthma Sleep Impact Scale, which was developed specifically for use in COPD populations. Ninety percent of the identified studies used one of two non-disease-specific sleep scales, ie, the Pittsburgh Sleep Quality Index and/or the Epworth Sleep Scale, although neither has been tested for reliability or validity in people with COPD.

Conclusion: The results highlight a need for existing non-disease-specific instruments to be validated in COPD populations and also a need for new disease-specific measures to assess the impact of sleep problems in COPD.

Keywords: sleep, symptom assessment, chronic obstructive pulmonary disease, systematic review

Introduction
 slept problems are a common and important, but poorly understood and under-researched, aspect of chronic obstructive pulmonary disease (COPD). After breathlessness and fatigue, sleep disturbance is considered to be the third most common symptom experienced by people with respiratory disease and is also predictive of exacerbations, respiratory-related emergency hospital visits, and all-cause mortality. Insomnia describes any reported difficulty a person has with sleep and has four elements: difficulties falling asleep, interrupted sleep, trouble staying asleep, and still feeling tired and worn out even after a usual amount of sleep. Around 10% of the adult population is affected by insomnia, but the occurrence is much higher in
people with COPD, where estimates range between 16% and 75%. The benefits of sleep are well known, and long-term interruption of normal sleeping patterns has a detrimental impact on physical, emotional, and social functioning, and is also associated with anxiety, depression, bodily pain, and a wide variety of pre-existing chronic medical conditions. In addition to insomnia, narcolepsy (suddenly falling asleep at inappropriate times), restless legs syndrome, and obstructive sleep apnea are the most common sleep disorders found in the general population, and people with COPD are disproportionately affected. Restless legs syndrome involves a need to move the legs, usually at night-time, is associated with marked sleep disturbance, and affects 7%–14% of the general population and 29% of patients with COPD. Obstructive sleep apnea is the periodic interruption of airflow in the upper airway during sleep and affects 3%–7% of the general population and 25%–29% of people with COPD. A summary of the occurrence of four common sleep disorders in COPD populations is provided in Table 1.

Given the importance of sleep disorders in COPD, being able to accurately classify their nature and severity is important in the management of COPD. Although self-reported sleep disorders are associated with COPD symptoms and poorer health-related quality of life, their relationship with traditional diagnostic markers of lung function (such as forced expiratory volume in one second, forced vital capacity, and oxygen saturation) is weak. This emphasizes the need for clinical instruments to accurately assess the impact of the disease and its treatment on a patient’s health and well-being through patient-reported outcome measures (PROMs) as well as recording changes in physiological function.

Many of the instruments that have measured sleep disturbance in epidemiological studies were originally developed for people with a range of psychological conditions and/or pre-existing sleeping disorders. However, the validity of these measures cannot be assumed to transfer between clinical populations. Thus, the aim of this review was to identify and evaluate the suitability of published measures of sleep disturbance for use in people with COPD in order to make recommendations for best practice for clinical and research purposes. Our objectives were to:

- Identify which patient-reported outcome sleep measures have been used in people with COPD
- Identify which instruments have been developed and validated specifically for people with COPD
- Summarize the evidence for reliability and validity of sleep instruments in COPD patients
- Examine associations with sleep disturbance recorded by sleep instruments used in clinical studies of COPD patients.

### Materials and methods

Ethical approval was not needed to undertake this review, which was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

### Search strategy

In this study, we conducted a systematic computerized literature review designed to identify all PROMs concerned with sleep problems experienced by people with COPD. The search included all instruments that had been developed and validated in people with COPD as well as generic instruments that had been developed for use in other disease areas and then administered to adult COPD patients.

**Stage 1: Identification of sleep outcome measures used in COPD**

The first stage of the search was to identify sleep outcome measures that had been used in COPD. This was conducted using EMBASE, MEDLINE, and PsycINFO electronic databases for all years up to May 2014 using both key words, ie, the Medical Subject Headings (MeSH) “COPD” AND “sleep” and expanded to include all recognized subheadings. All titles, abstracts, and full texts from the identified papers were examined by the lead author (APG) for reference to specific sleep instruments or data indicating that at least one sleep outcome measure had been used. A list of sleep outcome measures was then produced. The reference lists and citations of selected articles were also searched to identify any additional sleep PROMs not found by the electronic database search.

**Stage 2: Selection and evaluation of sleep instruments used in COPD**

A SCOPUS database search was carried out on each of the detected sleep outcome measures to identify all publications.
in which the original paper had been cited. The search included the following related terms:

1. Construct-related terms: sleep problems
2. Population terms: COPD patients (in the title, abstract, text, or reference section)
3. Outcome-related terms: development, validation, or psychometric properties of sleep PROMs designed specifically for people with COPD. Sleep outcome measures not specifically designed for people with COPD but used in a COPD patient group whether psychometric data were reported or not
4. Method-related terms: instrument* OR measure* OR question* OR scale OR assess
5. Quality assessment terms: valid* or reliab* or evaluat* OR psychometric.

We also screened the reference lists and citations of included articles to identify additional relevant publications.

Eligibility criteria
To be included in the review, all identified articles had to meet the following inclusion criteria: the article described PROMs that either had been specifically designed and validated for use in patients with COPD or included a generic instrument that had been administered to COPD patients; information on at least one measurement property of the outcome measure was reported; the study sample consisted of adults with a clinical diagnosis of COPD; a full text of the original publication was published electronically, in English, in a peer-reviewed journal.

Articles were excluded if reference to COPD and/or sleep only appeared in the text or reference section. Similarly, we excluded all articles with mixed study samples where the results from COPD patients were not reported separately. Review articles, protocols, and case studies were also excluded. Two investigators (APG and JY) read independently all titles, abstracts, and full texts of all the retrieved articles to determine which were eligible for review. Any disagreements were resolved at a consensus meeting.

Methodological quality assessment
The COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) checklist is a standardized tool for evaluating the methodological quality of PROMs. COSMIN checklists are used to evaluate the measurement properties of instruments in terms of their internal consistency, reliability, measurement error, content validity, structural validity, hypothesis testing, cross-cultural validity, criterion validity, and responsiveness to change. As it was anticipated that the number of PROMs that had been developed and validated for use in COPD populations was likely to be very small, rather than using the full COSMIN checklist we used four PROM characteristics recommended by the US Food and Drug Administration to evaluate the measurement properties of identified sleep PROM instruments in relation to their use in COPD patients, ie, conceptual and measurement model, reliability, validity, and responsiveness to change.

Conceptual model
Identified articles were examined for descriptions of concepts contained within the instrument, including the rationale and process for deriving scale scores from raw scores, identifying and dealing with floor and ceiling effects, and scale variability.

Reliability
Articles were scrutinized for estimates of reliability, including inter-item correlations, test-retest repeatability, internal consistency, and/or kappa statistics.

Validity
Any reference to content, construct, and criterion-related validity were noted. When considering construct validity, we also recorded methods to differentiate between people with different levels of lung function or disease severity, such as the Global Initiative for Chronic Obstructive Lung Disease staging system that classifies people with COPD according to the results of pulmonary tests. Where available, we also collected data regarding the relationships between sleep outcome instruments and other established COPD outcome measures (such as the St George’s Respiratory Questionnaire, the Medical Research Council Dyspnea scale, and routine clinical tests). Any analyses intended to examine dimensionality using factor analysis or Rasch analysis were noted, along with any assessments of differential item functioning that evaluated group differences in PROM item responses.

Responsiveness to change
All data relating to the ability of the instrument to detect changes over time in terms of sleep disturbance were noted. Where correlations between changes in scores of two measures are reported, these had to relate to predefined hypotheses.

Results
The stage 1 database search identified articles referring to COPD and sleep (Medline 804, EMBASE 2,314, and
PsycINFO 59) from which one COPD-specific and six non-disease-specific sleep instruments were identified (Table 2).

In stage 2, the SCOPUS search found 10,602 articles citing any of the seven sleep outcome measures, 270 of which referred to COPD. After applying the exclusion criteria, 44 manuscripts were selected for review (Figure 1). Nearly 90% of the reviewed publications either used the Pittsburgh Sleep Quality Index (PSQI; 19/44, 43.1%) or the Epworth Sleepiness Scale (ESS; 20/44, 45.5%).

Stage 1 Seven sleep instruments identified

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>SCOPUS references (n)</th>
<th>References to COPD (n)</th>
<th>Excluded</th>
<th>Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD and Asthma Sleep Impact Scale</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Basic Nordic Sleep Questionnaire</td>
<td>200</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Berlin Questionnaire</td>
<td>720</td>
<td>22</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>4,720</td>
<td>153</td>
<td>133</td>
<td>20</td>
</tr>
<tr>
<td>International Restless Legs Syndrome</td>
<td>548</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>4,144</td>
<td>71</td>
<td>52</td>
<td>19</td>
</tr>
<tr>
<td>Sleep Disorders Questionnaire</td>
<td>262</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>10,602</td>
<td>270</td>
<td>226</td>
<td>44</td>
</tr>
</tbody>
</table>

Abbreviation: COPD, chronic obstructive pulmonary disease.

Stage 2 Selection and evaluation of sleep instruments used in COPD

Figure 1 Flow diagram showing the total number of studies screened, assessed for eligibility and included in the review.

Abbreviation: COPD, chronic obstructive pulmonary disease.
the ESS assesses the likelihood of a person dozing off or falling asleep in eight common life situations. Most studies involved patients with moderate-severe COPD recruited from hospital outpatient or specialist respiratory clinics.

**COPD-specific sleep outcome measures**

After assessing the methodological properties of the identified PROMs, only one instrument appeared to have been developed and validated for use in COPD patients, ie, the COPD and Asthma Sleep Impact Scale (CASIS).²⁵

The CASIS is a seven-item measure of sleep impairment during the previous week. Five items relate to disturbance falling asleep or staying awake during the day. The remaining two items concern sleep quality. The items are scored on a five-point scale ranging from 0 if the item never applies, to 4 if the item applies very often. A total raw score is produced from the sum of the seven individual scores which is then linearly transformed to a 0–100 total scale score. A mean CASIS score of 43.3±24.7 was reported in patients with mild COPD. The results of the original psychometric testing of the CASIS (Table 3), showed that the scale had good internal consistency (Cronbach’s alpha 0.91), test-retest reproducibility (intraclass coefficient 0.84), and concurrent validity (correlated with the St George’s Respiratory Questionnaire, r=0.68).

**Table 3 Psychometric properties of COPD and Asthma Sleep Impact Scale**

<table>
<thead>
<tr>
<th>Conceptual and measurement model</th>
<th>Rationale for deriving scale scores</th>
<th>Items generated from focus group discussions in UK and US samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale structure</td>
<td>15 item scale scored 1= never to 5= very often – transferred onto a 0–100 scale</td>
<td></td>
</tr>
<tr>
<td>Variability</td>
<td>Mean score COPD patients (n=112) 47.1±24.0</td>
<td></td>
</tr>
<tr>
<td>Reliability</td>
<td>Not tested</td>
<td></td>
</tr>
<tr>
<td>Inter-intra observer repeatability</td>
<td>Item correlations</td>
<td>9 items highly correlated r&gt;=0.75; 6 items indicating item redundancy</td>
</tr>
<tr>
<td>Internal consistency</td>
<td>Cronbach’s alpha 0.91</td>
<td></td>
</tr>
<tr>
<td>Stability over time</td>
<td>2-week test-retest reproducibility ICC 0.84</td>
<td></td>
</tr>
<tr>
<td>Validity</td>
<td>Convergent validity</td>
<td>Correlated with SGRQ r=0.68 P=0.0001 Correlations between CASIS scores and number of bad days r=0.61, overall health status (0.5), and higher mean CASIS scores in COPD patients receiving oxygen treatment (51.4 vs 43.3) Correlates with living with COPD questionnaire 0.58</td>
</tr>
<tr>
<td>Responsiveness to change</td>
<td>Not tested</td>
<td></td>
</tr>
</tbody>
</table>

None of the non-disease-specific sleep scales reported any tests of reliability or validity to justify their use in the COPD population. Significant associations were observed in only 8/20 (40%) of studies where the ESS was compared with other COPD-related outcome measures. For example, the prevalence of daytime sleepiness (ESS >10) was significantly greater in patients diagnosed with insomnia.¹¹ Compared with people who had obstructive sleep apnea/hypopnea syndrome, COPD patients were more likely to be affected by daytime sleepiness.³² Significant differences in mean ESS scores were observed between patients with COPD and restless legs syndrome compared with controls who had restless legs syndrome.³³ However, no differences in daytime sleepiness were observed in a study that compared use of temazepam between COPD patients and controls.³⁴ Similarly, no significant differences in ESS scores were detected in patients with and without restless legs syndrome³⁵ (Table 4).

For the PSQI, significant associations were noted in 11/19 (57.9%) of the relevant studies. PSQI scores were found to be significantly higher in patients with restless legs syndrome.³⁶ PSQI total scores also correlated with total scores from the St George’s Respiratory Questionnaire³⁷,¹⁴ and the Fatigue Severity Scale.³⁸ In contrast, no correlation was observed between PSQI and St George’s Respiratory Questionnaire scores in an investigation of factors affecting health status in COPD patients with comorbid anxiety or depression.³⁹ Further, although significant PSQI score reductions were observed in patients receiving a course of cognitive behavioral therapy (where the primary outcome was insomnia),³⁹ no reductions in pre- and post-sleep quality were observed in a randomized controlled trial that compared cognitive behavioral therapy with usual care, where sleep was a secondary outcome measure to anxiety and depression⁴⁰ (Table 5).

Table 6 shows the papers that used the four remaining generic outcome measures in studies of COPD patients.³³,³⁵,⁴¹,⁴² With so few studies, there are currently insufficient data to evaluate the utility of these instruments; however, in one study,³³ International Restless Leg Study Group scores correlated significantly with ESS scores.

Although the results provide some evidence of the validity of measures of sleep disturbance in people with COPD, none of the above sleep measures were specifically evaluated for people with COPD. Similarly, we did not find any articles that provided data on test-retest, intrarater, or inter-rater reliability or responsiveness to change among COPD patient groups.
Table 4 Summary of studies that used the Epworth Sleepiness Scale

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study focus</th>
<th>COPD study sample</th>
<th>Measures of COPD severity</th>
<th>ESS (mean ± SD/ median and range)</th>
<th>ESS &gt; 10 (%)</th>
<th>Associations with ESS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aras et al</td>
<td>RLS symptoms in COPD patients during an exacerbation period</td>
<td>22 male inpatients</td>
<td>GOLD stage IV: FEV&lt;sub&gt;1&lt;/sub&gt;, 30% or 50% plus chronic respiratory failure; mean FEV&lt;sub&gt;1&lt;/sub&gt;, 39.4%; 95% CI</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Free thyroxine values negatively correlated with ESS (r&lt;sub&gt;=&lt;/sub&gt;-0.481, P&lt;0.043)</td>
</tr>
<tr>
<td>Bednarek et al</td>
<td>Prevalence of SDB and COPD in a representative urban sample aged 41–72 years</td>
<td>676 participants</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 0.7, 10.6%</td>
<td>6.4±3.9</td>
<td>Not reported</td>
<td>Mean ESS in people with excessive sleep disorder: men 12.6±2.0 versus women 12.9±2.4 (P&lt;0.05)</td>
</tr>
<tr>
<td>Budhiraja et al</td>
<td>Prevalence of insomnia in patients with COPD, and characteristics associated with insomnia in COPD patients</td>
<td>183 hospital patients</td>
<td>GOLD stage I, 3%; stage II, 39%; stage III, 29%; stage IV, 28%; % predicted post-bronchodilator FEV&lt;sub&gt;1&lt;/sub&gt; 45.9±18.6; FEV&lt;sub&gt;1&lt;/sub&gt;/FVC ratio 49.6±12.5</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Daytime sleepiness (ESS &gt;10) greater in patients with insomnia (36.5% versus 14.6%, P=0.004)</td>
</tr>
<tr>
<td>Cavalcante et al</td>
<td>Occurrence and associations with RLS in a COPD population</td>
<td>104 hospital outpatient attenders</td>
<td>Mean eSS in people with excessive sleepiness (36.5%) versus healthy controls (22.6%)</td>
<td>6.9±5.1</td>
<td>20.2</td>
<td>No difference in mean values between patients without RLS (6.6±4) versus with RLS (7.7±6.0). ESS positively correlated with BMI (P&lt;0.003)</td>
</tr>
<tr>
<td>De Lima et al</td>
<td>Whether clinically stable COPD patients without cognitive symptoms may present with subtle cognitive impairments</td>
<td>30 hospital outpatients</td>
<td>Mean FEV&lt;sub&gt;1&lt;/sub&gt;, 42.1±15.9</td>
<td>6.7±3.7</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kapella et al</td>
<td>Feasibility and assessment of the impact of a CBT intervention for people with COPD and insomnia</td>
<td>23 patients recruited from advertisements and word of mouth</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC ratio &lt;70%</td>
<td>9.2±5.0</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Karachaliou et al</td>
<td>Association between OSAHS-related symptoms and physician-diagnosed asthma and COPD</td>
<td>1,501 primary care patients (323 with COPD)</td>
<td>GOLD stage I, 28.8%; stage II, 53.3%; stage III, 15.2%; stage IV, 2.8%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Increased odds of people with COPD having an ESS score ≥10; OR 2.04, 95% CI (1.33–3.14)</td>
</tr>
<tr>
<td>Lewis et al</td>
<td>Variability of nocturnal desaturation in COPD over a 3-week period and impact the variability may have on clinical decision-making</td>
<td>26 stable COPD hospital outpatients</td>
<td>Mean post-bronchodilator FEV&lt;sub&gt;1&lt;/sub&gt;, 28.6%</td>
<td>4.1±6.2; range 0–11</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lewis et al</td>
<td>Prevalence and clinical impact of nocturnal desaturation in a typical COPD patient population with COPD</td>
<td>59 COPD outpatients</td>
<td>Mean predicted FEV&lt;sub&gt;1&lt;/sub&gt;, 37.2±14.9; FVC 1.9±0.9; FVC predicted 62.1±17.6; TB&lt;sub&gt;90&lt;/sub&gt; 38.4±34.9</td>
<td>5.0; range 2.0–8.0</td>
<td>Not reported</td>
<td>No significant difference between desaturators and non desaturators (P=0.88)</td>
</tr>
<tr>
<td>Lo Coco et al</td>
<td>Prevalence, severity, and associations with RLS in COPD patients</td>
<td>87 COPD outpatients</td>
<td>GOLD stage II, 42.5%; stage III, 40.2%; stage IV, 17.3%</td>
<td>8.98±3.89</td>
<td>Not reported</td>
<td>Significant difference in mean ESS score between COPD with RLS and controls with RLS 11.81±1.09 versus 8.62±3.66 (P=0.009)</td>
</tr>
<tr>
<td>McNicholas et al</td>
<td>Placebo-controlled, double-blind trial of severe, stable COPD patients comparing the effect of tiotropium on sleeping oxygen saturation</td>
<td>56 hospital outpatients</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;65% predicted; FEV&lt;sub&gt;1&lt;/sub&gt;/FVC &lt;70%; Awake pAO&lt;sub&gt;2&lt;/sub&gt;, &lt;9.98 kPa (75 mmHg) prior to entry</td>
<td>5.7 in intervention group versus 6.4 in control group</td>
<td>Not reported</td>
<td>None reported</td>
</tr>
</tbody>
</table>
Nunes et al\(^1\)  
Sleep quality in COPD patients at home using actigraphy and association between sleep quality and daytime somnolence  
26 hospital patients  
GOLD stage II, 50%; stage III, 38.5%; stage IV, 11.5%; FEV\(_1\)% predicted 47.6±16.04  
8.27±4.4  
61.5  
No difference between COPD and controls (8.27±4.4 versus 6.07±3.9, \(P=0.12\)). No difference in proportion with ESS ≥10 COPD (61% versus controls 86%, \(P=0.09\))

Oliveira et al\(^2\)  
Evaluate accuracy of a portable monitoring device in the detection of OSA in patients with COPD  
26 hospital outpatients  
FEV\(_1\)/FVC 0.6±0.10; FEV\(_1\)% post-BD 55±0.08; FVC% post-BD 77±8.9  
10.5±4.1  
Not reported  
None reported

Scharf et al\(^3\)  
Correlation between disturbed sleep and COPD  
180 pulmonary clinic patients  
GOLD stage I, 10.6%; stage II, 30.6%; stage III, 46.1%; stage IV, 12.8%. FEV\(_1\)% predicted 47.6±15.2  
7.0±4.8  
24.7  
No associations with ESS and other symptoms

Soriano et al\(^4\)  
Natural history of the most common respiratory chronic conditions, including COPD and OSA  
500 primary care patients  
GOLD stage I (27%); stage II (58%); stage III (15%)  
Not reported  
29.2  
None reported

Stege et al\(^5\)  
Effects of long-term use of a benzodiazepine (temazepam) on breathing, dyspnea, and gas exchange during sleep, sleep quality, and sleepiness  
14 respiratory clinic patients  
FEV\(_1\)% predicted 33.5±9.2; FEV\(_1\)/FVC\(_1\)% 32.7±13.0; FEV\(_1\)(L) 0.99±0.30  
6.0±4.0  
50.0  
No difference between temazepam (5.0±4.0) and controls (6.0±4.0; \(P=0.13\))

Toraldo et al\(^6\)  
Pattern of daytime clinical variables that distinguish desaturator patients from nondesaturator COPD patients using cluster analysis  
51 consecutive hospital patients  
FEV\(_1\)% predicted 53 (SE 1.5); FEV\(_1\)/FVC ratio 37.6 (SE 0.5); FVC% predicted 81.5 (SE 1.2); AH1 2.8 (SE 0.1). Daytime paO\(_2\) values 60–70 mmHg  
3.9 (SE ±0.1)  
None  
No difference between desaturators and nondesaturators, both 3.8 (± SE 0.4)

Toraldo et al\(^7\)  
Effect of regular use of nCPAP in patients with overlap syndrome  
12 hospital outpatients  
FEV\(_1\)% predicted 60.3±1.3; FEV\(_1\)/FVC\(_1\)% 69.5±0.7  
16.58±0.86  
Not reported  
Reductions in ESS score between baseline and 3 months (16.6±0.86 versus 11.7±0.46; \(P=0.0001\)), 3 months and 12 months (11.7±0.46 versus 5.7±0.4; \(P=0.0001\)), and 12 and 24 months (5.67±0.4 versus 4.75±0.49; \(P=0.033\))

Trauer et al\(^8\)  
Relationship between 24-hour oximetry and resting partial pressure of oxygen  
35 community-living patients  
GOLD stage II, 20%; stage III, 49%; and stage IV, 31%; FEV\(_1\)% predicted 37.5±13.2  
Median 4 (IQR 2.8)  
Not reported  
Negative correlation between ESS and time below 90% SpO\(_2\); 24 hours -0.18 (0.29); waking hours -0.13 (0.46); sleeping hours -0.17 (0.24)

Tsolaki et al\(^9\)  
Effect of non-invasive ventilation as an additional treatment for severe COPD patients  
24 hospital outpatients  
FEV\(_1\)% predicted 34.7±11.3; FVC% 50.8±15.7  
9.2±3.7  
Not reported  
Significant reductions in ESS score between baseline and 1 month in patients who received noninvasive ventilation (10.3 versus 4.9; \(P=0.0001\)). ESS was an independent predictor of the Mental Component Score of the SF-36 (\(P<0.001\)).

**Abbreviations:** AH1, apnea-hypopnea index; BD, bronchodilator; BMI, body mass index; CI, confidence interval; OR, odds ratio; COPD, chronic obstructive pulmonary disease; RLS, restless legs syndrome; SDB, sleep-disordered breathing; CBT, cognitive behavioral therapy; OSAHS, obstructive sleep apnea/hypopnea syndrome; mMRC, modified Medical Research Council Dyspnoea scale; FVC, forced vital capacity; FEV\(_1\), forced expiratory volume in 1 second; GOLD, Global initiative for Chronic Obstructive Lung Disease; SpO\(_2\), oxygen saturation; ESS, Epworth Sleepiness Scale; SE, standard error; pO\(_2\), oxygen partial pressure; pO\(_2\), arterial oxygen tension; IQR, interquartile range; T980%, time spent with saturation below 90%; SF-36, Short-Form 36 Health Survey; nCPAP, nasal continuous positive airway pressure; SD, standard deviation; OSA, obstructive sleep apnea.
Table 5 Summary of papers that used the Pittsburgh Sleep Quality Index

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study focus</th>
<th>COPD study sample</th>
<th>Measures of COPD severity</th>
<th>PSQI (mean ± SD)</th>
<th>PSQI &gt;5 (%)</th>
<th>Associations with PSQI score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akinci and Yildirim[27]</td>
<td>Associations between quality of life and breathlessness, fatigue, sleep quality, and FEV, % predicted in patients with COPD</td>
<td>79 stable hospital outpatients</td>
<td>FEV₁ (%) 51.5±16.1 (range 18–80); FEV₁/FVC (%) 63.4±9.3 (range 34.6–70.2)</td>
<td>7.1±3.9</td>
<td>Not reported</td>
<td>Correlations between SGRQ and PSQI total scores (0.428, P=0.001); daytime dysfunction (0.400, P=0.001); sleep disturbance (0.481, P=0.001); habitual sleep efficiency (0.271, P=0.05); sleep latency (0.309, P&lt;0.01); subjective sleep quality (0.421, P&lt;0.001) but not sleep duration or use of sleep medication</td>
</tr>
<tr>
<td>Aras et al[28]</td>
<td>RLS symptoms in COPD patients during an exacerbation</td>
<td>22 male inpatients</td>
<td>GOLD stage IV: FEV₁ 30% or 50%, plus chronic respiratory failure; mean FEV₁ 39.4±9.97 %; mMRC 0 (4.8%); 1 and 2 (48.1%); 3 (34.6%); 4 (12.5%)</td>
<td>6.0±3.81</td>
<td>Not reported</td>
<td>PSQI score was higher in patients with RLS symptoms (7.76±3.74) compared with patients without RLS symptoms (3.44±2.18; P&lt;0.05) PSQI correlated with Fatigue Severity Scale (P&lt;0.005). Patients with RLS had poor quality sleep (P&lt;0.002). PSQI score correlated with mMRC (P&lt;0.005); higher BMI (P=0.01); serum ferritin (P=0.005). mMRC and creatinine influenced PSQI sleep quality</td>
</tr>
<tr>
<td>Cavalcante et al[29]</td>
<td>Occurrence and associations with RLS in a COPD population</td>
<td>104 hospital outpatients</td>
<td>Mean FeV₁ 3.1±23.96; FEV₁/FVC % 7.1±4.3</td>
<td>59.6%</td>
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<tr>
<td>Hynninen et al[30]</td>
<td>Factors affecting health status in COPD patients with comorbid anxiety or depression</td>
<td>58 hospital outpatients/responders to newspaper advertisements</td>
<td>29 (50%) had mild-moderate COPD and 29 (50%) had severe/very severe COPD. Mean FEV₁ 53.7±23.96; 50% had FEV₁ ≥50%</td>
<td>Men 8.1±3.6; women 9.2±3.8</td>
<td>Not reported</td>
<td>PSQI total scores not correlated with SGRQ, PSQI daytime functioning correlated with SGRQ total (P=0.57; P&lt;0.001); symptoms (0.374, P=0.011); activity (0.364, P&lt;0.01); impact (0.56, P&lt;0.001). PSQI sleep disturbance correlated with SGRQ total (0.404 P&lt;0.01); symptoms (0.378, P&lt;0.01), and impact (0.409, P=0.01)</td>
</tr>
<tr>
<td>Hynninen et al[31]</td>
<td>Effect of CBT on anxiety and depression compared with usual care and associations with age and sex</td>
<td>25 hospital patients/respondents to newspaper advertisements</td>
<td>FEV₁ (%) 59.8±21.1</td>
<td>9.8±4.4</td>
<td>Not reported</td>
<td>No significant difference between pre- and post-treatment sleep quality or at 6 months follow-up as a result of the CBT intervention</td>
</tr>
<tr>
<td>Ito et al[32]</td>
<td>Prevalence and associations between depression and sleep disorders in COPD patients and whether depression and sleep disorders are risk factors for exacerbations, hospitalization, and mortality due to COPD</td>
<td>85 hospital patients</td>
<td>GOLD stage I, 21.2%; stage II, 38.8%; stage III, 28.2%; stage IV, 11.8%. Mean post-BD FEV₁ 1.6±0.7 L; FVC 3.3±0.9 L; FEV₁/FVC % 47.1±13.9</td>
<td>5.5±3.3</td>
<td>43.5%</td>
<td>PSQI scores higher in COPD versus non-COPD patients (5.5±3.3 versus 4.1±2.6; P=0.0076). An increase in RR in patients with COPD versus non-COPD controls (RR 1.82, 95% CI 1.03–3.22; P=0.042). A weak correlation between PSQI scores and CeSD scores (r=0.22; P=0.044). Annual number of exacerbations was higher in COPD patients with depression (3.3±3.5) compared with patients having sleep problems alone</td>
</tr>
<tr>
<td>Kapella et al[33]</td>
<td>Feasibility and impact of a CBT intervention for people with COPD and insomnia</td>
<td>23 patients recruited from advertisements and word of mouth</td>
<td>FEV₁/FVC ratio &lt;70% predicted. Mean FEV₁, % predicted 62±18; mean FEV₁/FVC 50±10</td>
<td>11.0±3.6</td>
<td>Not reported</td>
<td>PSQI scores reduced following COPD treatment (11.0±3.6 versus 6.5±3.4; P=0.0002). Within group effect size 1.02</td>
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<tr>
<td>Author(s)</td>
<td>Study Title</td>
<td>Sample Size</td>
<td>Data</td>
<td>PSQI Total Score</td>
<td>Comparison</td>
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<tr>
<td>Lewis et al.</td>
<td>Variability of nocturnal desaturation in COPD as measured by OPO and the impact the variability may have on clinical decision-making</td>
<td>26 stable hospital outpatients</td>
<td>Mean FEV$_1$ % 28.6±1.06</td>
<td>Not reported</td>
<td>No significant association between PSQI and resting pO$_2$ (P=0.89)</td>
<td></td>
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<tr>
<td>Lewis et al.</td>
<td>Prevalence and clinical impact of nocturnal desaturation in COPD outpatients</td>
<td>59 consecutive outpatient and pulmonary rehabilitation patients</td>
<td>FEV$_1 &lt; 60%$ predicted and FEV/FVC &lt;70% predicted; mean FEV$_1$, % predicted 37.2±14.9; mean FVC % predicted 37.2±14.9; mean FEV$_1$, 0.9±0.4 L FEV$_1 &lt; 60%$ predicted and FEV/FVC ratio &lt;70% predicted. Mean FEV$_1$, (L) 0.8±0.37; mean FVC (L) 2.1±0.65</td>
<td>Median 7</td>
<td>No significant difference in PSQI total score between desaturators and nondesaturators (8 [IQR 4.11] versus 7 [IQR 4.11]; P=0.63)</td>
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<tr>
<td>Nisbet et al.</td>
<td>Occurrence of overnight desaturation; if resting oxygen saturation predicts overnight desaturation and whether desaturation correlates with HRQoL and sleep quality</td>
<td>38 consecutive outpatient and pulmonary rehabilitation patients</td>
<td>FEV$_1 &lt; 60%$ predicted and FEV/FVC ratio &lt;70% predicted. Mean FEV$_1$, (L) 0.8±0.37; mean FVC (L) 2.1±0.65</td>
<td>7.1±3.99</td>
<td>No significant difference in PSQI total score between desaturators and nondesaturators (6.7±3.78 versus 7.1±3.99; P=0.82)</td>
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<tr>
<td>Nunes et al.</td>
<td>Impact of sleep quality on HRQoL in COPD</td>
<td>30 hospital COPD patients</td>
<td>GOLD stage II, 50.0%; stage III, 33.3%; stage IV, 16.7%; mean FEV$_1$, % predicted 48.55±17.27 FEV/FVC % 52.1±9.85</td>
<td>7.37±3.6</td>
<td>Significant positive correlation between PSQI total score and SGRQ total score (r=0.42; P=0.02) and impact domain score (r=0.47; P=0.01); global PSQI score was a predictor of SGRQ total score (adjusted r$^2$ 0.373, P=0.001) and SGRQ impact score (adjusted r$^2$ 0.329, P=0.001)</td>
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<tr>
<td>Nunes et al.</td>
<td>Sleep quality in COPD patients at home using actigraphy and association between sleep quality and daytime somnolence</td>
<td>26 stable respiratory outpatients</td>
<td>GOLD stage II, 50.0%; stage III, 38.5%; stage IV, 11.5%; mean FEV$_1$, % predicted 47.62±16.04</td>
<td>6.96±3.5</td>
<td>Mean PSQI total score significantly worse in COPD than in controls (6.96±3.5 versus 4.8±2.4; P=0.043); no significant correlation between PSQI and actigraphy variables</td>
<td></td>
</tr>
<tr>
<td>Oh et al.</td>
<td>Characteristics of fatigue in patients with chronic lung disease</td>
<td>128 hospital patients, 80% of whom had COPD, 13% had bronchiectasis, and 4% had interstitial lung disease</td>
<td>Mean FEV$_1$, 64.5±28.8</td>
<td>Mean score 1.9±0.7 (range 0–3)</td>
<td>In the regression analysis, sleep quality was not independently associated with fatigue; standardized β coefficient 0.02. t=0.25 P=0.8</td>
<td></td>
</tr>
<tr>
<td>Reisheit et al.</td>
<td>Impact of dyspnea, fatigue, and sleep difficulty on functional performance</td>
<td>30 home and 47 clinic patients</td>
<td>FEV$_1 &lt; 60%$ predicted; mean FEV$_1$, 41.2±11.79</td>
<td>8.69±4.33</td>
<td>Weak non-significant correlation between sleep difficulty and functional performance (r=0.17, P=0.05)</td>
<td></td>
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<tr>
<td>Scharf et al.</td>
<td>Extent of sleep problems in COPD; predictors of HRQoL and the contribution of sleep disturbance to HRQoL</td>
<td>180 pulmonary clinic patients</td>
<td>GOLD stage I, 10.6%; stage II, 30.6%; stage III, 46.1%; stage IV, 12.8%; mean FVC% predicted 64.7±16.3; FEV/FVC % 57.5±123; FEV/L 1.24±0.50 FVC (L) 2.17±0.70</td>
<td>11.0±5.4</td>
<td>HRQoL and SGRQ scores significantly associated with PSQI (adjusted r$^2$ HRQoL 0.24 and SGRQ 0.23 both P&lt;0.0001). HRQoL and SGRQ were independently associated with PSQI score (r$^2$ 0.06, P=0.0002 and r$^2$ 0.05, P=0.0005, respectively)</td>
<td></td>
</tr>
<tr>
<td>Suh et al.</td>
<td>Effect of anxiety on heart rate variability, depression, and sleep in COPD</td>
<td>30 COPD pulmonary rehabilitation patients and 30 non-COPD controls</td>
<td>COPD patients with anxiety PSQI I 2.0 (4.06) versus healthy patients with anxiety 7.8 (4.02) GOLD criteria: stage I 13.3%; stage 2, 43.3%; stage 3, 30%; stage 4, 13.3%</td>
<td>12.0±4.02</td>
<td>COPD patients with anxiety had poorer sleep quality than non-COPD controls with anxiety (12.0 versus 7.8; t=2.74, P=0.01). The COPD only group had significantly lower PSQI scores than COPD anxiety group (6.9 versus 12.0; t=−3.49, P=0.002)</td>
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</tbody>
</table>
Table 5 (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study focus</th>
<th>COPD study sample</th>
<th>Measures of COPD severity</th>
<th>PSQI (mean ± SD)</th>
<th>PSQI &gt;5 (%)</th>
<th>Associations with PSQI score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soler et al[^4]</td>
<td>PR improves sleep quality in chronic lung disease</td>
<td>46 obstructive, 13 restrictive, 5 mixed</td>
<td>FEV₁, % predictive obstructive 44.2 (12.3), Restrictive 82.2 (6.8), Mixed 62.7 (11.5)</td>
<td>6.6 (3.9) obstructive 8.2 (3.7) restrictive 6.6 (4.7) mixed</td>
<td>58</td>
<td>Poor sleep quality was reported by 58% of patients before PR and 47% after PR (P&lt;0.001)</td>
</tr>
<tr>
<td>Halvani et al[^2]</td>
<td>Evaluation of exogenous melatonin administration in improvement of sleep quality in patients with COPD</td>
<td>48 stable hospital patients</td>
<td>Confirmed diagnosis of GOLD stage II, GOLD stage IV</td>
<td>Intervention Not reported</td>
<td>Not reported</td>
<td>Melatonin group Baseline 11.6±3.96; follow-up 8.7±4.15 (P=0.002). Placebo group Baseline 10.6±2.48; follow-up 10.1±2.66 (P=0.065)</td>
</tr>
<tr>
<td>Bhatt et al[^3]</td>
<td>NPPV in subjects with stable COPD</td>
<td>15 stable hospital patients who received NPPV versus 12 controls</td>
<td>FEV₁/PF ratio &lt;0.70 PaCO₂ &lt;52 mmHg</td>
<td>3.7 (3.0) NPPV 6.1 (3.2) Controls</td>
<td>Not reported</td>
<td>Results after 6 months NPPV 3.7 (3.0) versus 3.4 (2.0; P=0.2) Controls 6.1 (3.3) vs 5.7 (3.2) P=0.77</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RLS, restless legs syndrome; mMRC, modified Medical Research Council Dyspnea scale; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range; nCPAP, nasal continuous positive airway pressure; PR, pulmonary rehabilitation; RR, relative risk; BD, bronchodilator; CBT, cognitive behavioral therapy; SD, standard deviation; NPPV, noninvasive positive pressure ventilation; PaCO₂, partial pressure of carbon dioxide; HRQoL, health-related quality of life; PSQI, Pittsburgh Sleep Quality Index; OPO, overnight pulse oximetry; SGRQ, St George’s Respiratory Questionnaire; CeSD, Center for Epidemiologic Studies Depression.

**Discussion**

Sleep disturbances are an important problem that can seriously impact physical and mental well-being as well as quality of life for people with COPD. This review identified seven outcome measures that have been used in COPD populations but none has been sufficiently validated to satisfy US Food and Drug Administration requirements. Only one measure, the CASIS, included item response theory in the instrument. Incorporating item response theory is now considered to be an essential component in the design and validation of all PROs.[^19]

The majority of sleep studies in COPD have relied on general measures of sleep dysfunction, the ESS and the PSQI, and although both of these instruments have been extensively used in a variety of clinical populations, neither has been validated for use in COPD patients. The ESS has been validated for use in COPD patients and has been used in a variety of clinical populations. However, as we did not search the non-English language journals, we have not identified all the main PROMs of sleep disturbance in COPD. A strength of this study was the comprehensiveness of our literature search. We have identified all the main PROMs of sleep disturbance in COPD patients. Nevertheless, until an accepted cutoff value for excessive daytime sleepiness is established, the cutoff value representing poor quality sleep is displayed on Figures 2 and 3. Most of the observed PSQI scores were above 5, ie, above the accepted cutoff value for excessive daytime sleepiness.[^28] Point and interval estimates for the PSQI are displayed on Figures 2 and 3. The point estimates of sleep disturbance from clinical studies of COPD patients using the ESS and the PSQI are shown on Tables 4 and 5. In 15 of 15 studies, the mean median scores were less than 10, ie, below the accepted cutoff value for excessive daytime sleepiness, with the cutoff value representing poor quality sleep being displayed on Figures 2 and 3. Point and interval estimates for the PSQI are displayed on Figures 2 and 3.
Table 6 Summary of articles using generic sleep measures

<table>
<thead>
<tr>
<th>Outcome measure and authors</th>
<th>Study focus</th>
<th>COPD study sample</th>
<th>Measures of COPD severity</th>
<th>Outcome reported (mean ± SD)</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin Questionnaire</td>
<td>Occurrence and associations with RLS in a COPD population</td>
<td>104 hospital outpatient attenders</td>
<td>mMRC 0 (4.8%); I and 2 (48.1%); 3 (34.6%); 4 (12.5%)</td>
<td>30 (29%) of patients had a high probability of OSA</td>
<td>Risk of OSA not associated with RLS (P = 0.25)</td>
</tr>
<tr>
<td>Cavalcante et al</td>
<td>Sleep quality and excessive daytime sleepiness in ambulatory patients with moderate to severe COPD</td>
<td>15 consecutive female clinic outpatients</td>
<td>FEV1 predicted &lt; 65% of daytime hypoxemia (PaO2 &lt; 10.0 kPa) and/or hypercapnia (PaCO2 &gt; 6.0 kPa); FEV1 % 36±12; FVC % 63±14; FEV1 (L) 0.73±0.45 (range 0.25–1.8); FVC (L) 1.3±0.45</td>
<td>BNSQ 9.9±3.0</td>
<td>BNSQ score higher than controls (9.9±3.0 versus 7.6±3.2; P=0.025) and correlated with insulin levels (r=0.59, P=0.027) and body movements (r=0.52, P=0.047)</td>
</tr>
<tr>
<td>Saarensanta et al</td>
<td>Prevalence, severity, and associations with RLS in COPD patients</td>
<td>87 COPD outpatients</td>
<td>GOLD stage II, 42.5%; stage III, 40.2%; stage IV, 17.3%</td>
<td>IRLSG score 32 (36.8%)</td>
<td>IRLSG score in COPD patients 20.5±2.8 versus 18.0±3.5 in controls (P=0.016); moderate correlation between ESS and IRLSG score (Spearman correlation 0.489, P=0.01)</td>
</tr>
<tr>
<td>Lo Coco et al</td>
<td>Differences in symptoms and polysomnographic parameters in COPD patients</td>
<td>52 consecutive hospital outpatients</td>
<td>FEV1 % predicted 60±10; FVC % predicted 93±12; FEV1/FVC 60±8</td>
<td>SA 36.0±6.9</td>
<td>COPD patients had higher scores in PLM (25.2±7.1 versus 21.1±6.2, P=0.0003) and PSY (18.0±6.0 versus 15.3±5.0, P=0.035)</td>
</tr>
<tr>
<td>SDQ Valipour et al</td>
<td>Differences in symptoms and polysomnographic parameters in COPD patients</td>
<td>52 consecutive hospital outpatients</td>
<td>PLM 25.2±7.1; PSY 18.0±6.0; Narcolepsy 22.1±5.5</td>
<td>Minimum SaO2 had an independent effect on SDQ subscale scores: SA (P=0.045), PLM (P=0.051), PSY (P=0.037), and narcolepsy (P=0.053)</td>
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</table>

**Abbreviations:** BNSQ, Basic Nordic Sleep Questionnaire; COPD, chronic obstructive pulmonary disease; PLM, periodic limb movement; SDQ, Sleep Disorders Questionnaire; PSY, psychiatric sleep disorder; RLS, restless leg syndrome; IRLSG, International Restless Leg Study Group; SA, sleep apnea; FVC, forced vital capacity; FEV1 forced expiratory volume in 1 second; OSA, obstructive sleep apnea; mMRC, modified Medical Research Council Dyspnea scale; GOLD, Global initiative for chronic Obstructive Lung Disease; SaO2, arterial oxygen saturation; ESS, Epworth Sleepiness Scale; PaCO2, partial pressure of carbon dioxide; PaCO2, hypercapnia PaCO2.
ESS ≥10 = cut-off score for excessive sleepiness

**Figure 2** Point estimates and variability in studies that used the ESS.
Abbreviation: ESS, Epworth Sleepiness Scale.

PSQI total score ≥5 = indicator of poor sleep quality

**Figure 3** Point estimates and variability in studies that used the PSQI.
Abbreviation: PSQI, Pittsburgh Sleep Quality Index.
waking up feeling rested. Only one item relates specifically to breathing problems, ie, shortness of breath, coughing, and chest tightness. Further, as these symptoms are all contained within the same item, it is not possible to differentiate patients who may have different severity of symptoms; for example, between patients who wake up at night only with shortness of breath or wake up with both shortness of breath and coughing. Since the publication of the original paper, the CASIS has not been used in any intervention studies, so further evidence is needed to confirm the utility of this instrument in guiding the clinical management of COPD patients and in research.

This review has highlighted the current reliance of sleep research on generic sleep measures and the paucity of disease-specific instruments currently available to assess the patient’s experience of sleep in relation to COPD. By definition, generic measures tend to cover broad aspects such as functional status and perceptions and are more likely to identify aspects that are not disease-related. Because instruments validated in one population may not perform well in specific populations under investigation, separate validation of generic measures in each population is recommended.43 Similarly, given that disease-specific measures are generally more responsive to change, outcomes based solely on generic measures are unlikely to detect treatment-related improvements.44 These deficiencies could call into question findings from previous research on the impact of sleep problems in COPD. The need for validated COPD-specific sleep outcome measures was emphasized in an expert panel meeting held in 2011.45 While appreciating the multifactorial nature of sleep disturbance in COPD, the panel highlighted the need for an instrument to classify patients according to their night or daytime symptoms, which is not possible using existing PROMs for sleep. Development work on new COPD sleep PROMs to address these limitations is currently being carried out by the authors of this review.

Conclusion
This review highlights the complexity of sleep assessment, the inadequacy of non-disease-specific measures to capture problems experienced by people with COPD, and the absence of robust and validated methods of assessing and classifying symptoms associated with disrupted sleep in COPD. In studies using non-disease-specific sleep measures, there is a pressing need for these to be validated with COPD populations and/or for new disease-specific PROMs to be developed.

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Author contributions
All authors contributed to the design of the review. APG carried out the literature searches, produced draft manuscripts for review, and edited the manuscript prior to submission. JY read and verified the suitability of the articles for review and also participated in consensus meetings. ST provided guidance and editorial support during preparation of the review. All authors contributed and approved the final version of the manuscript. ST and JY are guarantors of the paper, taking responsibility for the integrity of the work as a whole from inception to the published article.

Disclosure
The authors report no conflicts of interest in this work.

References


