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A Comprehensive Literature Review of COPD-Related Fatigue

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disease and major cause of disability. COPD may be considered a systemic disease, which causes an array of symptoms, one of which is the subjective sensation of fatigue. In recent years, COPD related fatigue (COPD-RF) has increasingly been recognised as an important area of research. The aim of this paper is to comprehensively review the literature concerning this topic and to summarise existing knowledge on the subjective perception of fatigue in people with COPD. This paper provides a narrative review of literature in this area. The search used the electronic databases of OVID MEDLINE and EMBASE included original studies from 1980 to December 2011. The databases were searched using the key MeSH terms COPD and Fatigue.

In total 40 relevant publications were identified. This literature review covers the following areas identified by research studies: fatigue in COPD in comparison with healthy older people, gender differences, patients' experience of fatigue, prevalence of fatigue reporting in COPD, pattern and frequency of fatigue in COPD, the impact of fatigue on an individual's life, predictors of fatigue, coping and treatment strategies for the management of fatigue. Furthermore, this review identifies areas for further research and makes recommendations for clinical practice.

Keywords

COPD – Chronic Obstructive Pulmonary Disease, Disease Management, Fatigue, Prevalence, Symptoms

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disease and a major cause of disability. Although the disease primarily affects the respiratory system, there are also major systemic consequences [1;2]. COPD causes an array of symptoms, one of which is the subjective sensation of fatigue. There are several studies addressing this perception of fatigue in COPD [3-5]. However, there are differences in definitions, interpretation and assessment of fatigue, resulting in confusion and making comparison between studies difficult. The sensation of fatigue may be defined in various ways as tiredness [6], lack of energy [7], exhaustion or weakness [8]. Studies identify fatigue in a variety of ways: as one of the symptoms of the disease [8;9], patients' complaint [7], a subjective multi-component experience [3;10], part of general health measure [11;12] or an independent variable affecting many areas of a patient's health and functioning [4;13]. Fatigue may be considered as an independent phenomenon with diverse manifestations, such as physical or mental tiredness, loss of attention, concentration or motivation [14]. There are also various theories [15], hypothesised models [4;16] and measurement of fatigue [17;18]. Consequently, with such a diverse interpretation of fatigue in COPD studies, there are many methods of assessment.

The aim of this literature review is to summarise existing knowledge concerning the subjective perception of fatigue in people with COPD. Using a comprehensive and systematic approach this review attempts to cover the following areas identified by research studies: fatigue in COPD in comparison with healthy older people; gender differences; patients' experience of fatigue; prevalence of fatigue reporting in COPD; pattern and frequency of fatigue in COPD; the impact of fatigue on an individual's life; predictors of fatigue; coping and treatment strategies for fatigue management. Furthermore, this review identifies areas for further research in COPD-Related Fatigue (COPD-RF) and makes recommendations for clinical practice.

Methods

This paper provides a narrative review of literature in this area. The search strategy used the electronic databases of OVID MEDLINE and EMBASE. The databases were searched by using the key MeSH terms 'COPD' and 'Fatigue'. Studies from 1980 to December 2011 were included in the search. The titles and abstracts of all obtained studies were assessed and relevant studies identified. In addition, the reference lists of the obtained articles were examined for additional publications. Only original quantitative and qualitative studies in English language, which involved a COPD population and considered assessment of fatigue as a subjective sensation were included. Meta analyses were considered. Concept analyses and descriptive review papers as well as studies focused on muscle fatigue mechanisms were excluded.

Results

Search for literature in OVID found 647 papers, however, most of them irrelevant or considering skeletal and respiratory muscle fatigue measures. After abstract assessments and search for duplicates 33 papers were identified. Further reference screening added 5 more papers. Moreover, one Cochrane review and conference data relevant to the subject were included. In total data from 40 papers were extracted and reviewed.

Comparison of subjective fatigue between patients with COPD and healthy older people

A fundamental question concerning fatigue in COPD relates to age adjusted norms; is fatigue a feature of the disease or is it merely a reflection of ageing? There were three studies, which considered comparison of fatigue between COPD patients and healthy subjects. Theander and Unosson [19] addressed this specific question in a comparison study between 36 COPD patients and 37 healthy age-matched subjects. The assessment consisted of severity, frequency, duration and functional impact of fatigue (Fatigue Impact Scale (FIS), validated by Theander and colleagues [20]). In all components of fatigue assessment COPD patients had significantly higher scores compared with healthy controls. However, 40% of the subjects in the control group had illnesses other than COPD and consequently, may not be considered 'healthy'. Moreover lung function was not measured in either the COPD or control group and accurate characterisation of control group or the disease severity was not possible. More recently Baghai-Ravary and colleagues [13] studied 107 patients with moderate COPD and 30 healthy controls. The groups were adequately age-matched and subjects or patients with a history of other significant diseases were excluded from both groups. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F) Scale. This unidimensional scale was originally developed for cancer patients and is untested in a COPD population. In this study, COPD patients scored significantly lower on the FACIT-F scale than healthy controls, indicating higher levels of fatigue that are unrelated to age. However, this unidimensional tool gives only general results about fatigue and provides little information on particular aspects of fatigue such as mental or physical components. Finally, published data from Lewko *et al.* [21] compared a multidimensional fatigue score between 74 mild-to-severe COPD patients and 35 healthy age-matched subjects. There were no significant differences between groups according to age, BMI and body conposition. For this study the Multidimensional Fatigue Inventory (MFI-20) was used to measure 5 components of fatigue: general, physical, mental, reduced activity and motivation. The results indicated that all dimensions of fatigue are significantly impaired in COPD patients compared with healthy people of a similar age. In summary, two adequately powered studies suggest that fatigue is an independent feature of COPD. For details see table 1.

Table **1**. Comparison of fatigue between COPD patients and healthy older people - evidence summary

First author	**Year published**	**Study type**	**Sample size**		**Control group**	**Mean age (SD)**	**% pred. FEV_1 (SD)**	**Fatigue assess. tool**	**Tool type**	**Fatigue comparison**	**General comments**
			COPD	**Control**		**COPD v. Healthy**					
Theander[20]	2007	Cross-section study	36	37	age-matched general population (15 with a diagnosis of non-COPD chronic conditions)	Men 68 (5.3) and women 63 (4.6) v. Men 66 (5.2) and women 62 (5.8)	data not available	FIS	multi-dimension	all dimensions of fatigue significantly increased in COPD v. Healthy (p<0.001, cognitive fatigue p<0.05)	small sample size, control group non disease free, FEV_1 not assessed
Baghai-Ravary [13]	2008	Cross-section study	106	30	age-matched, no COPD or other respiratory disease, FEV_1/FVC >70%, no malignant, immunodeficiency or significant inflammatory disease	69.4 (8.2) v. 68.6 (6.1)	53.1 (21.1)% v. 94.1 (16.9)%	FACIT-Fatigue	uni-dimension	Increased fatigue in COPD compared to healthy (p=0.001)	adequate sample size, healthy age-matched control group
Lewko [21]	2009	Cross-section study	74	35	age-matched no airway obstruction, no significant inflammatory co-morbidities or unstable angina, no psychiatric diagnosis or mobility limitations	69.9 (8.4) v. 67.1 (8.8.)	46.5 (20.0)% v. 96.5 (13.2)%	MFI-20	multi-dimension	all dimensions of fatigue are significantly increased in COPD compared with healthy control (p <0.001)	adequate sample size, healthy age-matched control group

% pred. FEV_1: percent predicted Forced Expiratory Volume in one second; FEV_1/FVC : ratio Forced Expiratory Volume in one second / Forced Vital Capacity; FIS: Fatigue Impact Scale ; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy- Fatigue; MFI-20: Multidimensional Fatigue Inventory

Gender differences in fatigue

One study [7] of 56 male and 48 female stable COPD patients investigated fatigue using a self designed scale and the fatigue subscale of Short Form 36 (SF-36) questionnaire. They found no significant differences in fatigue according to gender. However, the women were significantly younger and with more severe airway limitation when compared to men. In addition the tool used lacked validation in the population. Other study [4] of adequately matched COPD men (n=68) and women (n=62) used a range of fatigue assessment tools including Numeric Rating Scale (NRS), Profile of Mood Scale (POMS) and Fatigue Assessment Inventory (FAI). Gender differences were seen in selected areas of the assessment. Fatigue was more intensive and distressing in women than in men and situation specific FAI score was similarly higher in women. However, there were no gender differences for other fatigue assessments. Although these authors assessed fatigue in a variety of ways there was no evaluation of physical or mental components. A recent large study by Theander and Unosson [22] investigated fatigue with respect to gender in COPD and healthy groups. Three hundred forty five COPD patients (150 male) were asked to indicate the frequency, duration and severity of fatigue and to complete FIS. Mean age (SD) for COPD male and female was statistically significantly different (65 (7.9) and 63 (8.3) years, respectively). There were no significant differences in fatigue between COPD men and women, as oppose to the findings in healthy subjects. However, it is difficult to know whether gender difference would have persisted if the groups were adequately age-matched. In one other study [21], there was also no evidence of differences in fatigue according to gender in COPD patients, although this was a secondary outcome of this study and characterisation of gender groups was inadequate. For study details see table 2.

In summary, there is some evidence based on data of limited quality currently available to suggest that men and women with COPD are equally affected by fatigue. However, women may experience more intense and distressing fatigue than men.

Table **2.** Gender differences in fatigue- evidence summary.

First author	Year published	Study type	Sample size		Study population	Mean age (SD)	% pred. FEV_1 (SD)	Fatigue assess. tool	Tool type	Fatigue comparison	General comments
			Male	Female		Male v. Female					
Gift [7]	1999	Cross-section study	56	48	stable COPD, not smoking, no psychologic diseases	62 v. 58	24 v. 20%	fatigue scale, SF-36 fatigue	self-design, subscale of QoL scale	no gender differences	Not validated tool used, significant age and FEV_1 differences between men and women
Kapella [4]	2006	Cross-section study	68	62	moderate-to severe stable COPD, FEV_1 predicted <70%, no Asthma, surgery or Pulmonary Rehabilitation recently	69.5(5.8) v. 68.7(6.7)	44.5 (17.9)% v. 46.1 (18.4) %	NRS-fatigue, POMS-Fatigue, FAI	Uni and multi-dimension	fatigue intensity and distress, FAI situation specific higher in women, no gender differences for POMS-F, NRS fatigue, other FAI scores	relevant sample size, variety of fatigue tools, but no physical and psychological dimensions included
Lewko [21]	2009	Cross-section study	52	22	stable COPD, no other significant co-morbidities	total 69.9 (8.4)	total 46.5 (20.0) %	MFI-20	multi-dimension	no gender differences	age and FEV_1 for men and women separately not published
Theander [22]	2011	Cross-section study	150	193	COPD, 75 yrs old or younger	65(7.9) v. 63(8.3) (p=0.01)	data not available	FIS	multi-dimension	no gender differences	large sample size, significant age difference between men and women, no FEV_1 measured

% pred. FEV_1: percent predicted Forced Expiratory Volume in one second; SF-36: Short Form 36; QoL: Quality of Life; NRS: Numeric Ratio Scale; POMS-F: Profile of Moods Scale- Fatigue; FAI: Fatigue Assessment Inventory; FIS: Fatigue Impact Scale; MFI-20: Multidimensional Fatigue Inventory.

Subjective experience of fatigue in COPD

Since fatigue is a subjective experience, it is inevitably perceived differently amongst individuals. One qualitative study on 17 COPD patients [5] used a structured interview to elucidate further patient perception of fatigue; these mild-to-severe patients described feeling generally tired; reported a lack of energy and a decreased ability to concentrate. Patients indicated that fatigue was present in conjunction with “laboured breathing” and brought on by activities such as climbing the stairs, walking uphill or by environmental factors, such as tobacco smoke or cold and windy weather. Importantly, the COPD subjects indicated that the feeling of fatigue occurs more quickly and after lower intensity exertion compared to fatigue experienced by a healthy person.

In another study exploring subjective fatigue in COPD, Kapella and colleagues [4] reported that 70% of patients stated that “current fatigue is different in quality and intensity than the fatigue they experienced before developing this condition [COPD]” and that fatigue did not predate any other symptoms. Only half of male participants indicated that exercise brought about fatigue (52%) but that fatigue was reduced by rest (73%), sleep (75%) or cool temperature (68%). Ream and Richardson [23] explored the experience of fatigue in 6 COPD subjects. One subject described fatigue as a feeling of ‘exhaustion’, which followed strenuous physical activity and was accompanied by aching. Patients complained of poor concentration and lack of “get up and go”, which may be considered as dampened motivation. Fatigue evokes the feeling of depression, constant low mood and low self-esteem. Patients reported that due to their fatigue and illness, they did not feel in control and missed “the person they used to be” before their illness. Inevitably fatigue contributes significantly to impaired quality of life (QoL) in patients with COPD and as a multi-component symptom reflects aspects of motivation, physical ability, mood states and cognitions.

The prevalence of fatigue in COPD

There are various studies investigating the prevalence of fatigue in COPD; however methodological differences in studies have led to differing results. Factors of importance include disease severity and stability, time from last exacerbation, co-morbidities and differences in assessment of fatigue itself. In an early study of Kinsman and colleagues [8], the Bronchitis-Emphysema Symptom Checklist (BESC) was used to examine the frequency of fatigue symptoms. One hundred and forty six patients were asked during their hospitalisation, how often they experienced fatigue “during periods of difficult breathing”. The study reported a high prevalence of fatigue with

91% of patients complained of experiencing fatigue at least sometimes and 43% “almost always” and “always”. However, in this study, patients were reporting fatigue as a feature of an exacerbation limiting the generalisation to a stable population; in addition the patients were poorly characterised. Using the same tool, Graydon and colleagues [24] assessed 71 severe COPD patients at 6-month intervals for 2.5 years. Fatigue prevalence in this cohort of patients was between 59% initially and 62% at final assessment and did not increase significantly over time, supporting the idea of lower (although still clinically relevant) levels of fatigue during a period of relative stability.

In a later study by Gift and Shepard [7], a self design questionnaire was used and validated by correlation with the SF-36 fatigue subscale in 104 COPD severe patients. Fifty eight percent of patients reported experiencing a lack of energy during previous week. The authors also suggested that a combination of fatigue and dyspnoea led the patients to seek health care. This was confirmed in a recent study of Vandevoorde *et al.* [6], which included 146 smokers aged 40-70 yrs old from GP surgeries. Only 17% had a confirmed diagnosis of COPD while just fewer than 30% were newly diagnosed after performing a spirometric assessment. Subjective symptom of fatigue was assessed using a question ‘Are you tired more easily than before?’. The prevalence of fatigue was around 47% for all COPD patients, but was significantly higher in the group with previously known COPD (68%) compared with the newly detected cases (35%). Although the method of fatigue assessment can be criticised and the reported prevalence may be subject to error, this study showed fatigue as an important independent factor, which may help detect COPD in a high risk population.

Walke and co-workers [25] assessed a fatigue symptom using the modified Edmonton Symptoms Assessment Scale (ESAS) in 74 COPD patients, and followed this up after 24 months. Fatigue, together with shortness of breath and physical discomfort, were the most prevalent symptoms. The prevalence of fatigue was 69% (50% moderate-to-severe) at the beginning and 92% (62% moderate-to-severe) at the end of the study. It was in contrast with previously reported findings [24]. However, the study population was older than in previous studies and inclusion criteria indicate higher severity of airflow obstruction. Another study of Walke group [9] used the ESAS in 81 COPD of patients and recorded lower fatigue prevalence of 49%. This prevalence was, however, comparable to previous study’s report on moderate-to-severe fatigue. Yet it remains unclear whether the difference derived from this change of reporting criteria. A similar prevalence was reported in a recent study of Peters *et al.* [26]. The study included 168 stable moderately severe COPD with mean age of 64.5. Fatigue was measured using a subscale of the Checklist Individual Strength (CIS). Abnormal (>26) fatigue score was present in 47.6% of patients including 24.4% of severely fatigued patients. Furthermore, half (n=77) of these patients were followed up after 4 years. In this sub-cohort the percent of abnormal fatigue increased from 45.5% to 63.7% at follow up. Fatigue score increased in over 30% of patients and severe fatigue was reported in 41.6%. This study provides the longest fatigue follow up data, showing an increase in fatigue over the time. These variations in prevalence may be further explained by differences in co-morbidities or disease severity between studies or follow up time.

Another study investigated symptoms distress and QoL in advanced COPD [27]. The study assessed 100 COPD patients with severe airways limitation using the Memorial Symptom Assessment Scale (MSAS). The instrument assessed prevalence, frequency, severity and degree of symptoms and included 'lack of energy' subscale. Lack of energy was the second most prevalent symptom, just after shortness of breath, and it was reported by 71% patients.

A review of symptoms prevalence in end stage COPD and other chronic diseases [28] revealed that 68-80% patients complained of fatigue and it was the second most prevalent symptom after dyspnoea. It was a less common symptom than in cancer patients, and similar to that of patients with heart disease or AIDS. In a more recent study focusing on the last year of life of COPD patients [29], fatigue was experienced by 96% of patients. For detailed information see table 3.

In conclusion, fatigue prevalence ranged from 35% in newly diagnosed patients, 48% in mild COPD, 58-69% in patients already diagnosed, 71% in more advanced disease, 92% during 'difficult breathing' or disease exacerbation and 96% in palliative patients. The prevalence of fatigue in COPD progresses with time and disease advancement. Prevalence and perception of fatigue in COPD is clearly dependent upon authors' definition, assessment method or/and disease severity; however the clinical importance of assessing fatigue may be undervalued presently.

Table **3.** The prevalence of fatigue in COPD - evidence summary.

First author	Year published	Study type	Sample size	Study population	Mean age (SD)	% pred. FEV_1 (SD)	Fatigue assess. tool	Tool type	Fatigue prevalence	General comments
Kinsman [8]	1983	Cross-section study	146	chronic bronchitis and emphysema, during period of hospitalization	63 (9)	data not available	BESC	symptom checklist	91%	no current diagnostic criteria and no FEV_1 measures, data collected during acute exacerbation
Graydon [24]	1995	Cohort prospective, 2.5 years longitual	71	COPD, FEV_1 <50%	66.57	31.7 (8.6)%	BESC	symptom checklist	58.6-61.8% (not significant change)	the tool not tested for sensitivity to change, only moderate-to-severe patients included
Gift [7]	1999	Cross-section study	104	COPD, non-smoker, no psychological disease	60	22.6(6.8) %	a fatigue scale	self-design NRS tool	58%	54% of patients were using oxygen either continuously or occasionally, poor validation of the tool
Walke [9]	2004	Cross-section study	81	COPD, $PCO_2 \geq 45$ mmHg or SpO2 ≤ 90%, cor pulmonale, history of respiratory failure or respiratory hospitalisation	72 (7)	data not available	ESAS	symptom checklist	49%	Disease severity unclear, COPD patients had similar fatigue prevalence to cancer (48%) and CHF patients (42%),
Elkington [29]	2005	retrospective, post mortem carer survey	209	last year of life	76.8	data not available	VOICES	survey, including symptom list	96%	recall from the carer 5-10 month after the death may create a bias

Solano [28]	2006	review	285 2 studies	advance COPD, end of life	71 (1 study only)	data not available	no validated tool	semi structured interviews and survey	68 and 80%	data based only on 2 studies using different method of assessment
Walke [25]	2007	cohort , 2 years longitual	74	COPD, hospitalisation in last 6 months, having any 2 of: PCO2 ≥ 45 mmHg, SpO2 ≤ 90% or cor pulmonale or FEV_1 <0.5 or polycythemia	72 (7)	data not available	ESAS	symptom checklist	69-92% (moderate-to-severe 50-62%)	Data from 45 patients available as 29 patients deceased during the study. Age and disease severity of this sub cohort unclear
Vandevoorde [6]	2007	population, Cross-section study	68	smokers, age 40-70, COPD with FEV_1/FVC < 70%	53.9 (8.9)	77.5 (16.5) % for newly diagnosed COPD	GP completed questionnaire	symptom checklist	47.1% (34.9%-68%)	Not validated tool used
Blinderman [27]	2009	Cross-section study	100	advance COPD, FEV_1 <30%, no psychiatric or cognitive disorder	62.2 (10.5)	24.4 (3.9)%	MSAS Lack of energy	multi-dimensional symptom evaluation	71%	no fatigue specific assessment used
Peters [26]	2011	cohort , 4 years longitual	168, 77 after 4 years	moderate COPD, no exacerbation in 6 months, no pulmonary rehab	64.5 (9.1)	51.6 (13.6)%	CIS	fatigue subscale, symptom checklist	47.6%, after 4 years 63.7%	adequate sample side, no fatigue specific assessment with a cut point not validated for COPD

% pred. FEV_1: percent predicted Forced Expiratory Volume in one second; BESC: Bronchitis-Emphysema Symptom Checklist ; ESAS: Edmonton Symptoms Assessment Scale; MSAS: Memorial Symptom Assessment Scale; CIS: Checklist Individual Strength ; GP: General Practitioner.

Pattern and frequency of fatigue in COPD

How often fatigue occurs and whether there are diurnal patterns to its presentation are further research areas. In one study on 104 COPD subjects, where fatigue was identified as a "lack of energy", there were on average 2.7 reports per week of fatigue [7]. In another, qualitative study [5], fatigue was reported to occur every day, intermittently throughout the day. In advanced disease, frequency of 'lack of energy' is similar to that of breathlessness; 67% of patients described it as 'frequently' or 'almost constant'[27].

The daily pattern of fatigue is difficult to discern; it may be present in the evening "after a day with usual activities"[4] or in may worsen in the afternoon (51%). Half of the responders could not determine morning or afternoon prevalence of fatigue. However, one study of temporal variations of symptoms in COPD [30] assessed the pattern of fatigue over 8 days. Ten patients were asked to rate their fatigue using the Visual Analogue Scale (VAS) at 5 time points a day. A circadian rhythm was identified with fatigue peak time at 16.16 hr, with a 95% confidence interval ranging from 14.36 to 17.40 hours. These findings are consistent with some patients' reports from a previous study [4].

In conclusion, currently available data concerning frequency of fatigue are confusing and fragmented. There are some indications from a small study that fatigue peak occurs in the afternoon. However, there is not enough evidence to draw generalised conclusion.

Fatigue impact on patients' health

Fatigue has been recognised as an important and common symptom of COPD, which might negatively impact patients' functional status. In patients with mild-to-moderate COPD increased fatigue is associated with a higher sick leave from work [31] and higher frequency of exacerbations [4;13]. A recent study [32] showed that higher VAS-fatigue was associated with higher disability level in COPD. Fatigue showed negative associations with the functional performance [4;33]. However, it is not clear in what way fatigue may contribute to impairment in patients' functional performance. A model analysis by Kapella and colleagues [4] showed that fatigue, dyspnoea, airflow limitation and anxious mood, directly affected patients' functional performance. However, according to other study using structural equation modelling [12]. fatigue influenced functional performance only indirectly via its impact on negative mood and health perception. This association between fatigue and negative mood was indicated by another regression study [34]. However, due to a small sample size the findings could not be considered conclusive.

Further research shows that patients with COPD report a combination of breathlessness and fatigue, leading to a gradual decline in their Activities of Daily Living (ADLs) [5]. Although fatigue did not interfere directly with family or friend relationships, it limited social roles. However, in a recent study, it was shown that abnormal fatigue levels affect functional impairment, QoL and relationships in COPD patients [26]. This in turn may impact on an individual's activities outside home. In one study, fatigue was the only predictor of reduced time spent outdoor [13]. However, in a recent study by Peters *et al.* [26] physical activity measured by accelerometer was not affected by fatigue. This discord may be due to differences in patients' perception of activity done and accelerator measures.

Moreover, patients who report severe fatigue had more limitations in cognitive, physical and psychosocial functioning (FIS) and worse health related QoL (SF-36), compared with those with no fatigue [35]. The impact of fatigue on QoL in COPD has been frequently evaluated with authors showing significant relationships between higher fatigue and reduced QoL [3;13;36]. Fatigue or lack of energy is a recognised component of QoL measures [11] and may be assessed as one of its subscales. However, this may be an oversimplified approach; an examination of a pathway analysis model for variables associated with chronic bronchitis and emphysema revealed that fatigue did not influence directly QoL nor functional status, but was a mediator of QoL impairment through mood disturbance [37]. Prospective testing of this proposed model is warranted.

Predictors of fatigue in COPD

Few studies have focused on investigating causes of fatigue in COPD using standardised questionnaires [3;4;7;10;13;38;39]. The use of uni- and multidimensional measures has influenced presented results. Furthermore, some studies identified associations between fatigue and other variables based only on simple coefficient correlations, which could not be as robust as multivariante analysis.

Generally the studies report an association between fatigue and dyspnoea [4;7;10;13;39;40]. Significant correlations were found between unidimensional measures of fatigue and dyspnoea regardless of severity of disease [4;7;39]. There was also a significant mild-to-moderate correlation between all dimensions of MFI-20 and Baseline Dyspnoea Index, where lower score indicates higher dyspnoea (r= -0.27 for Mental fatigue to –

0.53 for Physical Fatigue) [10]. However, these studies are limited by the lack of multiple regression analysis and adjustment for confounders. The results are, therefore, indicators of direction rather than predictors of fatigue.

Kinsman and collegues [8] used a dyspnoea severity classification (alike Medical Research Council (MRC) scale) to evaluate possible associations between fatigue and dyspnoea severity. There were significant differences found in the frequency of fatigue (BESC) between groups. These findings have been confirmed in another study [13], where fatigue was assessed using the FACIT-F questionnaire and significant differences in fatigue according to the MRC grades were found. In other study [21] using MFI-20, differences according to MRC dyspnoea grades were evident only for selected dimensions and were not present for Reduced Motivation and Mental Fatigue.

Recently, one small study by Inal-Ince group [36] investigated patients' fatigue severity and its impact, in relation to a grading indices of COPD severity. The BODE and SAFE indices were used to determine patient severity groups [41;42]. The study assessed 22 mild-to-very severe COPD males (mean age 62.5 (6.5)) and showed significant correlations between fatigue severity (FSS) or fatigue impact (FIS) scales and both BODE and SAFE indices. Although the finding indicates association between fatigue and grades of disease severity, it is underpowered and a choice of the statistical analysis for a 4-stage grading system may be criticised.

Moreover, fatigue is related to mood and stress [10], depression [4;10;13] and indirectly to anxiety [4]. Depression has been shown to be a significant predictive factor in the fatigue regression analysis [4;13].

Recently an association between fatigue (Manchester COPD-fatigue questionnaire) and a range of inflammatory markers (IL-6, CRP, TNF-α, TNF-α-R1 and TNF-α-R2) in 120 moderate COPD patients were explored [43]. There were no significant correlations found between fatigue and any of the markers. However, Borg exertion score (RPE) after a walk test correlated weakly with TNF-α only ($r=0.23$, $p=0.01$) and at rest with both TNF-α and CRP ($r=0.24$, $p=0.01$ and 0.19, $p=0.05$, respectively). These findings may suggest that although chronic fatigue is not directly correlated with systemic inflammation in COPD, there is some association between this inflammation and acute sensation of tiredness at rest and on exercise.

Furthermore, fatigue is associated with age [4;44] annual exacerbation rate [4;13], sleep quality [4;10], walking test distance [3;39] and muscle strength [38]. A recent large Pan-European study [45] assessed subjective fatigue (FACIT-F) in 1817 COPD patients from a primary care population in 7 European countries. A wide range of mild-to-severe COPD patients with mean FEV_1 % predicted 56.7(20.1) and average age 64.9 were included, 13% of them had acute exacerbation. Fatigue was significantly worse in patients with an exacerbation and in patients with 3 or more co-morbidities, but not with cardiovascular co-morbidity alone.

Nevertheless, studies using a multidimensional assessment of fatigue provide us with more detailed data about relationships between dimensions of fatigue and their associates. Each of these variables are associated with selected components of fatigue. For example there was a mild significant correlation between sleep quality (Pittsburg Sleep Quality) and General, Physical and Mental Fatigue dimensions of MFI-20 but not with Reduced Activity [10]; whereas, 6 Minute Walk Test correlated significantly only with Reduced Activity, General and Physical dimensions [3] and muscle strength only with Physical Fatigue [38]. In a study using unidimensional fatigue assessment, no relationship was evident between fatigue and airway obstruction [4;13]. However, with more comprehensive assessment of fatigue using the MFI-20, showed that % predicted FEV_1 was related to all but Mental Fatigue dimensions [3;10]. Furthermore, there were significant differences in scores for Physical Fatigue and Reduced Activity dimensions only, when stratified according to GOLD spirometric stages [21].

One recent study [44] of 42 older COPD patients aged 72.9± 6.5 years, who were participating in a Pulmonary Rehabilitation (PR) programme examined multidimensional fatigue and the relationship between fatigue dimensions and anxiety, depression, sleep quality, dyspnoea and other physiological factors. There was a moderate, statistically significant correlation between age and Reduced Activity (r=0.43; p=0.05) and Reduced Motivation (r=37; p=0.05). Furthermore, anxiety had a significant but negative correlation with the motivational dimension (r=-0.47; p=0.01). In contrast with other studies, in this group of COPD patients there was no correlation between sleep quality, depression, walking distance or dyspnoea and any dimensions of fatigue. This may be explained by the much greater age of the study cohort. Moreover, the study group was not homogenous, with patients presented different advancement levels of rehabilitation as both very advanced and novice patients were included. Therefore, the findings have to be treated with caution as dynamicity and variation of the group has to be considered. See more studies’ details in table 4.

Table **4.** Correlates of fatigue in COPD- evidence summary.

First author	Year published	Study type	Sample size	Study population	Mean age (SD)	% pred. FEV_1 (SD)	Fatigue assess. tool	Tool type	Correlates	General comments
Kinsman [8]	1983	Cross-section study	146	chronic bronchitis and emphysema, during period of hospitalization	63 (9)	data not available	BESC	symptom checklist	MRC	correlation used for analyses of grading scales, non-stable disease data, not current diagnostic criteria
Breslin [3]	1998	Cross-section study	41	stable COPD	62 (8)	35.8(16.6) %	MFI-20	multi-dimension	FEV_1 % pred. and 6MWT (only GF, PF &RA); depression (GF&MF)	small sample size, multiple analyses without correction
Breukink [38]	1998	Cross-section study	19	stable COPD	64 (6)	38 (17) %	MFI-20	multi-dimension	FEV_1 (RA, RM), Borg dyspnoea and exertion (RM), upper & lower muscle strength	very small sample size, multiple analyses without correction
Gift [7]	1999	Cross-section study	104	stable COPD, not smoking, no psychologic diseases	60	22.6(6.8)%	fatigue subscale SF-36	subscale of QoL scale	dyspnoea, BSI physical symptoms, BSI somatisation	severe disease COPD, multiple parametric tests used for nonparametric data without correction
Woo [39]	2000	Cross-section study	37	chronic bronchitis, emphysema, no psychiatric or neuromuscular disease	66.9 (10.6)	48.1 (13.6)%	POMS-F	subscale of the Profile of Moods	6MWT (negative), Dyspnoea (VAS)	Pilot study- small sample size, not fatigue specific tool used
Oh [10]	2004	Cross-section study	128	stable COPD, no major co-morbidities	64.2 (11.3)	64.5 (28.8)%	MFI-20	multi-dimension	Overall fatigue: FEV_1 % pred., BDI, pulmonary symptom, mood, stress, sleep quality	no correction for multi-correlation analyses

Kapella [4]	2006	Cross-section study	130	moderate-to severe stable COPD, FEV_1 pred. <70%, no Asthma, surgery or PR recently	68.7(6.7) - 69.5(5.8)	44.5 (17.9)%- 46.1 (18.4) %	NRS fatigue, POMS-F	subscale of the Profile of Moods, numerical scale	NRS: age, no. of resp. Infection; NRS & POMS-F: dyspnoea, anxiety, depression, sleep quality	not well validated tools used, multiple parametric testing were used without correction
Baghai- Ravary [13]	2008	cohort study	107	stable COPD, FEV_1/FVC <70%	69.4 (8.2)	53.1 (21.1)%	FACIT-Fatigue	uni-dimension	dyspnoea (MRC, VAS), depression (CES-D), exacerbation rate	parametric analyses were used for non parametric data
Inal-Ince [36]	2010	Cross-section study	22	male only stable COPD	62.5 (6.5)	49.7 (28.5) %	FSS, FIS	multi-dimension	BODE, SAFE	correlation used for analyses of grading scales
Wong [44]	2010	Cross-section study	42	COPD participating in Pulmonary Rehabilitation	72.9 (6.5)	47.8 (16.3)% - only for n=14	MFI-20	multi-dimension	age (RA, RM), negative correlation with anxiety (RM)	Not homogenous population, during intervention process.
Jones [45]	2011	population, Cross-section study	1817	40-80 yrs COPD, no other respiratory or unstable cardiovascular disease	64.9 (9.6)	56.7 (20.1)	FACIT-Fatigue	uni-dimension	number of co-morbidities, but not associated with presence of cardiovascular co-morbidity	Large epidemiological study, fatigue was a secondary outcome only. Differences in fatigue between the co-morbidity groups were analysed
Al-shair [43]	2011	Cross-section study	120	stable COPD	66 (6.7)	52.5 (18.5)%	MCFS	multi-dimension	IL-6, CRP, TNF-α, TNF-α-R1 and TNF-α-R2 do not correlate with fatigue	adequate sample size, not clear if correction was used for multiple correlation analyses

% pred. FEV_1: percent predicted Forced Expiratory Volume in one second; 6MWT: 6 Minute Walk Test; BDI: Beck Depression Inventory; BESC: Bronchitis-Emphysema Symptom Checklist; CRP: C – Reactive Protein; FACIT-F: Functional Assessment of Chronic Illness Therapy- Fatigue; FIS: Fatigue Impact Scale; FSS: Fatigue Severity Scale; IL 6: Interleukin 6; MCRS- Manchester COPD Fatigue Score; MFI-20: Multidimensional Fatigue Inventory (GF- General Fatigue, PF – Physical Fatigue, RA- Reduced Activity, RM- Reduced Motivation, MF- Mental Fatigue subscales); MRC: Medical Research Council Dyspnoea Grade; NRS: Numeric Rating Scale; POMS-F: Profile of Moods Scale- Fatigue; PR: Pulmonary Rehabilitation; TNF-α: tumor necrosis factor-alpha (R1 &2: receptorn1& 2); VAS: Visual Analogue Scale.

In 4 studies, the robust multiple regression analyses were used to identify predictive variables of fatigue. Using a stepwise regression analysis 42% of the variance of fatigue (SF-36 fatigue) was explained by dyspnoea (self reported measure) and physical symptoms (MSAS) [7]. A later study of 128 moderate COPD patients, also identified dyspnoea together with mood as predictive factors (R^2=0.47) [10]. Similarly, around 40% of fatigue in men was explained by dyspnoea and depression and in women by dyspnoea, depression and sleep quality [4]. Other study indicated that predictive factors of fatigue are annual exacerbation rate and time spent outdoor [13]. However, the reduced time outdoor may be considered as a consequence of fatigue rather than its predictor. Nevertheless, these studies may be criticised for either lack of validated tools or choice of linear regression for non-continuous variables. Furthermore, none of these studies explored predictive factors considering the multidimensional nature of fatigue. One recently published study revealed that fatigue in COPD, when considered as a multi-component construct, can be explained by a different combination of variables [21]. This study drew together the psychological and physiological aspects of fatigue to develop working models of COPD-RF by using comparative data from healthy age-matched subjects. Logistic regression analyses were used to explore possible predictors of fatigue components of the MFI-20. Predictors of General Fatigue were depression, muscle strength and end SpO_2 (R^2= .62); of Physical Fatigue: depression, % predicted $FEV_{1,}$ Shuttle Walk Test and age (R^2= .57); of Reduced Activity: % predicted FEV_1, BMI and depression (R^2= .36); of Reduced Motivation: end SpO_2, depression and RPE (R^2 = .37) and of Mental Fatigue: depression and end SpO_2 (R^2= .38). This study highlighted the importance of the multi-component construct in exploring the mechanisms of COPD-RF. For more details see table 5.

In conclusion, the causes of fatigue may be sought in a combination of several psychological and physiological factors, which reflects the multidimensional nature of fatigue. However, only the minority of studies explored predictors of fatigue using multivariate analysis. It appears that a combination of depression, exercise capacity, muscle strength, airway limitation, blood oxygenation, BMI, dyspnoea and sleep quality may predict different dimensions of COPD-RF. Although, hitherto research goes some way towards explaining the mechanistic pathways of fatigue in COPD, there are many areas requiring further elucidation.

Table **5**. Predictors of fatigue in COPD according to regression analyses- evidence summary.

First author	**Year published**	**Study type**	**Sample size**	**Study population**	**Mean age (SD)**	**% pred. FEV_1 (SD)**	**Fatigue assess. tool**	**Tool type**	**Regression type**	**Regression predictors**	**General comments**
Gift [7]	1999	Cross-section study	104	stable COPD, not smoking, no psychologic diseases	60	22.6 (6.8)%	fatigue subscale SF-36	subscale of QoL scale	stepwise multiple	SF-36 fatigue: dyspnoea, physical symptoms (42%); lack of energy: physical symptoms, BSI somatisation and dyspnoea (66%)	Not validated tools used for regression analysis
Kapella [4]	2006	Cross-section study	130	moderate-to severe stable COPD, FEV_1 predicted <70%, no Asthma, surgery or Pulmonary Rehabilitation recently	68.7(6.7) - 69.5(5.8)	44.5 (17.9)%- 46.1 (18.4) %	NRS fatigue	numerical grading scale	stepwise multiple	For men: CRQ dyspnoea, depressive mood; in women: sleep quality, CRQ dyspnoea, depressive mood	Not validated tools used for regression analysis
Baghai-Ravary [13]	2008	cohort study	107 (86 in regression)	stable COPD, FEV_1/FVC <70%	69.4 (8.2)	53.1 (21.1)%	FACIT-Fatigue	uni-dimension	multiple linear	time spent outdoors, VAS dyspnoea, exacerbation rate, CES-D	linear regression was used for non-continuous variables
Lewko [21]	2009	Cross-section study	59	stable COPD, no other significant co-morbidities	69.9 (8.4)	46.5 (20.0) %	MFI-20	multi-dimension	stepwise logistic	GF: HADS depr., muscle torque, post exercise SpO_2; PF: HADS depr., % pred. FEV_1, ISWT, age; RA: % pred. FEV_1, BMI, HADS depr.; RM: Borg exertion, HADS depr., post exercise SpO_2; MF: HADS depr., post exercise SpO_2	Arbitrary fatigue cut point, multi-dimension fatigue analyses, small sample size for selected regression analyses

% pred. FEV_1: percent predicted Forced Expiratory Volume in one second; BSI: Brief Symptom Inventory; BMI: Body Mass Index; CES-D: Centre of Epidemiological Studies Depression Scale; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale (depr: depression); ISWT: Incremental Shuttle Walk Test; NRS: Numerical Rating Scale; QoL: Quality of Life; SF-36: Short Form 36; FACIT-F: Functional Assessment of Chronic Illness Therapy- Fatigue; MFI-20: Multidimensional Fatigue Inventory (GF- General Fatigue, PF – Physical Fatigue, RA- Reduced Activity, RM- Reduced Motivation, MF- Mental Fatigue subscales); $Sp0_2$: Blood oxygen saturation; VAS: Visual Analogue Scale

Coping and treatment strategies for fatigue

As has been shown earlier fatigue is an important and highly prevalent symptom in COPD, which can persist over time. Hence, the majority of patients develop some coping strategies. Over time when disease progresses, patients appear to learn how to accept and even cope with the feeling; "It upsets me but I am not going let it depress me" [5]. In addition, patients with COPD and asthma develop problem- and emotion-focused strategies. The most commonly used problem-focused strategies identified by patients were pacing, protecting oneself, and maintaining activities within limitations (energy conservation); regular exercising and keeping active (energy utilisation) and resting and relaxation (energy restoration). Both COPD and asthma patients found helpful methods of managing their emotional response to the problem: 53% of patients used a 'positive approach', 42% accepted their condition and physical limitations, other methods used were distracting (25%) and normalising (36%). However, for some patients, fatigue remained an important problem with reports of 'constantly fighting fatigue' or complaints of 'tired of being tired'.

One recent study evaluated an effect of breathing exercises on fatigue in COPD patients [46]. The study included 60 older (>70years) COPD in-patients. Patients were randomised to either experimental or control groups with routine treatment and assessed using the FSS. Patients in the experimental group had to perform respiratory exercises 4 times a day for 10 days; these included pursed lips breathing, diaphragm respiration and effective cough. There was no difference in FSS between the groups at baseline and the majority (90%) experienced severe fatigue. After 10 days fatigue had significantly diminished in both groups with much higher decrease in the experimental compare with control group. The reduction in fatigue sensation may be due to decreased work of breathing by using well established breathing control and chest clearance techniques in patients during exacerbation of COPD. However, the study is generally of poor quality, lacking clear explanation of randomisation, the tool validation method (there are a few references missing) or the cohort descriptive data. Therefore, the findings of this study are very difficult to interpret and cannot be regarded as robust evidence. Nevertheless, effective therapeutic strategies are required which will help patients to relieve unpleasant symptom of fatigue. One meta-analysis by Lacasse and colleagues [47] demonstrated that the fatigue subscale of a QoL measure is significantly improved followed a PR programme. Moreover, one congress report of fatigue following a course of PR confirms that the number of fatigued patients can be significantly reduced after PR [48]. However, a small randomised control trial of 26 severe COPD patients showed that after 12 weeks of PR there were no significant improvements for fatigue (FIS) in either rehabilitation and control groups

[49]. Nevertheless, there were no changes reported for other outcome measures and the study was underpowered with only 12 patients completing PR. Although there are some indications that PR may be one of the clinical interventions attenuating fatigue in COPD patients, it is not clear which elements of this comprehensive programme may play any role in the treatment process of fatigue. A recent observational study looked at fatigue in 251 COPD as a secondary result of a large PR randomised trial [50]. Fatigue was assessed by the SF-36 vitality and a cut point for a high fatigue was determined arbitrary prior the study. Thirty nine percent of patients (n= 97) had high fatigue at baseline. Regrettably, there is no data presented for SF-36 vitality in follow up and it is unknown how many patients changed their score after PR. Nevertheless, after 3 months of PR, high fatigue patients improved significantly compared to those with low fatigue on QoL scale. However, unlike in the low fatigue group, the improvements in a walked distance or endurance time achieved at the end of PR were not sustained after 1 year in the high fatigue group. This may suggest that fatigue is an important factor in long-term exercise tolerance maintenance. Therefore, fatigue management strategies may be crucial for long term benefits of PR. Nevertheless, the study uses one of the subscales of a generic QoL questionnaire for fatigue assessment. Hence, the results may give some indications for future research rather than being valid findings. See studies' summary in table 6.

In summary, coping strategies appear to be used by patients for management of fatigue and fatigue may be altered by PR. However, there is a lack of good quality RCTs to indicate the effectiveness of treatments of multidimensional fatigue.

Table **6.** Coping and treatment strategies for fatigue- evidence summary.

First author	Year published	Study type	Sample size	Study population	Control group	Mean age (SD)	% pred. FEV_1 (SD)	treatment/ strategy	Fatigue Tool	Effect	General comments
						Intervention v. Control					
Small [5]	1999	qualitative	17	COPD	no	62.8 (9.9)	34.8 (18.9) %	pacing, protection, energy conservation, keeping active, resting	Open question interview	not assessed	Focus group consists both COPD and asthma patients
Lacasse [47]	2007	meta-analysis	326 intervention v. 292 control	COPD home base, in- and out- patient,	usual care	not presented	not presented	4-52 weeks Pulmonary Rehabilitation	CRQ fatigue	statistically significant improvement the intervention group	No fatigue specific assessment included
Peters [48]	2008	cohort study	159	COPD	no	data not available	data not available	Pulmonary Rehabilitation	CIS	significant reduction in number of fatigued patients after intervention	only congress abstract published, no fatigue specific assessment
Theander [49]	2009	RCT	12 intervention v. 14 control	COPD, ≤75yrs old, 25-60% pred. FEV_1	yes	66 (6) v. 64 (6)	35.1 (7.6) v. 32.3 (9.5)%	12 week Pulmonary Rehabilitation	FIS	no significant improvements in either intervention or control	study underpowered, there were no improvements in any outcome measures
Zakerimoghadam [46]	2011	semi-experimental	30 intervention v. 30 control	hospitalised mild-to-moderate COPD, no psychotic confusion	routine treatment	data not available	data not available	Breathing exercises	FSS	significant reduction in number of fatigued patients after intervention	unclear randomisation method or cohort characteristics

Baltzan [50]	2011	cohort study	251	COPD, low and high fatigue groups	no	63.7(9.2)-67.1(8.2)	43.1 (12.6)-45.9 (13.3) %	3 month Pulmonary Rehabilitation	SF- 36 vitality	both low and high fatigue groups improved on all outcomes, but High fatigue did not sustain exercise tolerance improvement in 1 year	secondary analysis of RCT, no fatigue specific assessment

% pred. FEV_1: percent predicted Forced Expiratory Volume in one second; CIS: Checklist Individual Strength; CRQ: Chronic Respiratory Questionnaire; FIS: Fatigue Impact Scale; FSS: Fatigue Severity Scale; SF-36: Short Form 36

Discussion and conclusions

This literature review revealed that fatigue is a highly prevalent symptom in COPD, which may negatively impact patient's functional performance and QoL, affects ADLs or time spent outdoor. The review identified that fatigue is higher in COPD compared with healthy subjects and all components of fatigue may be affected. Although the studies' findings are consistent, they were based on few publications with sometimes flawed data, particular when considering a selection of healthy subjects. Future data obtained from larger population studies may widen knowledge regarding differences in fatigue between COPD and healthy populations. Interestingly, unlike in healthy population where women experience more fatigue [51], most of the studies presented in this review revealed no gender differences in fatigue in COPD population. This may indicate that mechanisms involved in fatigue in COPD equally affect both men and women. However, fatigue experience may be more intense and distressing for COPD women compared to men [4], it is similar to health population.

Furthermore, this literature showed that various patho-physiological and psychological factors may contribute to the increased fatigue in COPD. There was a strong indication that factors such as dyspnoea and depression may be predictors of fatigue. Depression is common co-morbidity in COPD [52] and inevitably affects all aspects of fatigue. Also, dyspnoea and fatigue are both syptoms of COPD [8] and they share some similar assessment features [53] or pathophysiological mechanisms. This includes involvement of the CNS and central fatigue [54;55], anxiety-depression disorders [52], hypoxaemia and hypercapnia, early lactic acid onset, skeletal and respiratory muscle weakness [53;56]. Other factors indicated by research to be involved in COPD-Related Fatigue are age, airway obstruction severity, exacerbation rate, sleep quality, exercise tolerance and muscle strength. More comprehesive anlyses of psychological, physical, behavioral and motivational fatigue revealed that each component could be explained by different variations. For instance, physical performance factors such as muscle strength or distance walked were associated more with physical and general aspects of fatigue; psychological factors such as depression and measure of oxygen level were associated with motivational and mental fatigue. Although presently there is no consensus regarding the mechanistic pathways of fatigue in COPD, there are some indications for future investigation of fatigue pathomechanism.

Furthermore, various fatigue coping methods are identified by patients, but there is little knowledge about management and treatment strategies focusing on this important and debilitating symptom. Pulmonary Rehabilitation, a well established treatment method for COPD [2] showed improvement in fatigue component of

QoL [47]. However, the studies evaluating specifically subjective fatigue in COPD failed to unambiguously confirm similar improvement. Future well-powered randomised trials will bring insight to this area of research. Some other areas identified by research, such as intensity, pattern and frequency of fatigue, lacked good quality data or showed contradictive findings to draw clear conclusions.

Concluding, data extraction and analysis for this review was particularly difficult as authors' definition of fatigue, tools and interpretation differed between most of the studies. This paper reveals lack of unity and consistency within literature of COPD-Related Fatigue and future research should use validated and fatigue specific assessment tools to provide more robust data in this area. This review draws all relevant knowledge and systematise existing evidence for clinical and research use. Gaps identified in literature may help develop future research studies and treatment strategies for COPD-Related Fatigue.

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Conflict of Interest

Authors declare no conflict of interest

List of Abbreviations:

ADLs: Activities of Daily Living

BESC: Bronchitis-Emphysema Symptom Checklist

CIS: Checklist Individual Strength

COPD: Chronic Obstructive Pulmonary Disease

CRP: C- Reactive Protein

ESAS: Edmonton Symptoms Assessment Scale

FACIT-F: Functional Assessment of Chronic Illness Therapy- Fatigue

FAI: Fatigue Assessment Inventory

FEV_1 : Forced Expiratory Volume in one second

FIS: Fatigue Impact Scale

FSS: Fatigue Severity Scale

GOLD: Global Initiative for Chronic Obstructive Lung Disease

IL 6: Interleukin 6

MCRS- Manchester COPD Fatigue Score

MFI-20: Multidimensional Fatigue Inventory

MRC: Medical Research Council Dyspnoea Grade

MSAS: Memorial Symptom Assessment Scale

NRS: Numeric Rating Scale

POMS: Profile of Moods Scale

PR: Pulmonary Rehabilitation

RPE: Borg Exertion Scale

QoL: Quality of Life

SF-36: Short Form 36 (generic QoL questionnaire)

TNF-α: tumor necrosis factor-alpha

TNF-α-R1: tumor necrosis factor-alpha receptor 1

TNF-α-R2: tumor necrosis factor-alpha receptor 2

VAS: Visual Analogue Scale

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