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Extra-pulmonary manifestations of COPD and the role of pulmonary rehabilitation: a symptom-centered approach

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Extra-pulmonary manifestations of COPD and the role of pulmonary rehabilitation: a symptom-centered approach

Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a complex and heterogenous disease that is associated with a range of respiratory and non-respiratory symptoms, which highly contribute to the daily burden of the disease. Symptoms burden remains high despite optimal bronchodilator therapy, but pulmonary rehabilitation (PR) is an effective intervention to improve patients' symptoms. A comprehensive interdisciplinary approach within the framework of a PR program is warranted to tackle these complex symptoms and their consequences.

Areas covered: This narrative review describes how symptoms of dyspnea, fatigue, cough, sputum, anxiety, depression, pain, sleep disturbances and cognitive decline arise in COPD and can contribute to several non-pulmonary manifestations of the disease. It also describes evidence of the effectiveness of interdisciplinary PR programs to counteract these symptoms. A literature search was performed on PubMed and Scopus between June and July 2020.

Expert opinion: Respiratory and non-respiratory symptoms are highly prevalent, often not comprehensively assessed, and result in several extra-pulmonary manifestations of the disease (physical, emotional and social). Interdisciplinary PR programs can improve these negative manifestations through different pathways, contributing for an effective symptoms' management. A thorough assessment of symptoms (beyond dyspnea) should be routinely performed, and may support the identification of treatable traits, allowing the tailoring of PR interventions and assessment of their real-life impact.

Keywords: COPD; dyspnea; fatigue; cough; sputum; anxiety; depression; pain; sleep disturbances; cognitive decline

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [1]. Although COPD primarily affects the lungs, there is now general consensus that it is a complex and heterogeneous disease with multiple pulmonary and extra-pulmonary manifestations [2-5], such as skeletal muscle dysfunction and postural issues [6], leading to a range of symptoms which highly contribute to the daily burden of the disease [7-9].

Over 80% of patients with COPD experience daily respiratory symptoms [7,10]. The cardinal symptom is dyspnea, but coughing and increased sputum production and retention are also present in a large proportion (23–87%) of patients [7,9,11-14]. Respiratory symptoms occur even in mild disease and may develop before the onset of airflow limitation [1,11]. The frequency and intensity of respiratory symptoms in each individual vary within and between days, being early morning and daytime symptoms the most prevalent [7,9,10,15]. It is often unrecognized that patients with COPD are very susceptible to fatigue and pain [8,16]. A subjective feeling of fatigue or general tiredness is prevalent in 35–96% of patients, across different studies [17] and, although not yet recognized by the Global Initiative for Chronic Obstructive Lung Disease, pain affects 32–85% of patients with COPD [16,18,19].

High levels of dyspnea and fatigue, presence of cough and increased sputum production and retention have been associated with disease progression, impaired health-related quality of life, problems to perform daily activities, impaired sleep quality, increased symptoms of anxiety and depression and increased mortality [7,9,14,20-25]. Anxiety and depression are more common in patients with COPD than in the general population or in patients with other chronic diseases, with a prevalence of 13–46% and 10–42%, respectively [26]. Symptoms of anxiety and depression, pain and respiratory symptoms, contribute to sleep disturbances and poor sleep quality [27-30], which affects 36–85% of patients with COPD [31,32]. Dyspnea, anxiety, depression and sleep disturbances have been related with cognitive decline (i.e., reports of memory deficits, related confusion and impaired cognition) [33-38]. Symptoms of cognitive decline have been increasingly recognized in patients with COPD, with a prevalence four times higher than matched healthy controls, and might be an additional barrier to the management of these patients and their participation in daily and social activities [33-36,39-43].

Symptom burden remains high despite optimal bronchodilator therapy [44]. Pulmonary rehabilitation (PR) is defined as a comprehensive non-pharmacological intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors [45]. A true comprehensive PR program has been described as a Swiss army knife, a multitargeted approach in which, based on the comprehensive assessment, patients' physical, emotional and social treatable traits (i.e., characteristics that are clinically relevant, identifiable and modifiable/treatable [46,47]) are identified and addressed within PR with an interdisciplinary team [48]. A comprehensive interdisciplinary approach adding targeted non-pharmacological interventions to pharmacological treatment in the framework of PR is therefore warranted to tackle these complex symptoms of COPD [45,48].

This review aims to describe how the main symptoms of COPD arise and can contribute to several extra-pulmonary manifestations of the disease, and describes evidence of the effectiveness of an interdisciplinary PR approach to counteract these consequences (Figure 1). A literature search was performed on PubMed and Scopus, between June and July 2020, using a combination of keywords related to COPD, symptoms and pulmonary rehabilitation.

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2. Dyspnea

Dyspnea is a cardinal symptom in COPD and a major cause of disability, affecting 59–92% of the patients [13,49]. It is defined by the American Thoracic Society as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [50], and it is usually seen as the result of the mismatch between increased inspiratory neural drive and inadequate mechanical response of the respiratory system [51].

Patients with COPD first perceive and report dyspnea during physical activity [52]. During exertion, there is an increase in metabolic carbon dioxide output, which stimulates peripheral and central chemoreceptors, leading to an increase in inspiratory neural drive and ventilation [51,52]. The known dynamic hyperinflation in COPD leads to a rapid and shallow breathing pattern, which results in functional limitation of inspiratory muscles, decreased dynamic lung compliance and inspiratory capacity, and worsening pulmonary gas exchange [49,51,52]. This constriction in tidal volume expansion, simultaneously with an increased/persistent chemostimulation, is perceived by patients as an unpleasant respiratory sensation, i.e., dyspnea [51]. Patients reduce their physical activity levels and adopt a sedentary lifestyle to avoid exertional dyspnea [49,51,52]. This leads to skeletal muscle deconditioning and deterioration of exercise capacity, which in turn lowers the threshold at which patients feel dyspnea during exertion (i.e., dyspnea appears at progressively lower exercise intensities), starting a vicious circle of dyspnea-inactivity [49,51,53]. The decline in physical activity is a strong predictor of mortality in patients with COPD [54]. Exertional dyspnea and the ventilatory limitations are key contributors to patients' impaired exercise tolerance, which is further limited by muscle dysfunction, cardiovascular and nutritional imbalances, and psychological factors [55-57].

Dyspnea is the symptom that concerns patients with COPD the most [58]. The anticipation of dyspnea triggers an emotional response of dyspnea-related fear, which activates fear-related areas of the brain and physiological fear responses, and is a mediator of anxiety and a contributor to an increased risk of depression, negatively impacting on patients' psychological well-being [49,52]. This emotional response of fear further contributes to decreased physical activity and worsens deconditioning, resulting in a downward spiral of inactivity, social isolation, fear, symptoms of anxiety and depression [26].

Altogether, dyspnea progression and all associated impairments result in decreased health-related quality of life [51,52]. Further, dyspnea levels are significantly correlated with 5-year survival in patients with COPD [59]. Alleviating symptoms of dyspnea is therefore essential in COPD.

International recommendations state that, after optimization of bronchodilator therapy, PR (including promotion of physical activity) is fundamental for an effective dyspnea management [50,51]. A systematic review with meta-analysis of 65 randomized controlled trials demonstrated clear clinically relevant benefits of PR relieving dyspnea symptoms in patients with COPD [60]. PR does not act directly in the improvement of lung mechanics or gas exchange; instead it optimizes the function of the other systems (e.g., muscular, skeletal systems), hence effects of lung dysfunction are diminished [61]. Several mechanisms contribute to the positive effects of PR on dyspnea. Exercise training reverses deconditioning by inducing changes in skeletal muscle biochemistry, improving its aerobic function [61]. This results in decreased lactic acidosis for a given level of exercise, reducing its ventilatory demand and, consequently, the inspiratory neural drive [51,61]. The decreased ventilatory requirements allow a slower respiratory rate, with a longer expiratory time, resulting in less dynamic hyperinflation and reduced dyspnea on exertion [50,51,61]. Exercise also results in central desensitization to dyspnea, although the mechanisms are not fully understood [61,62]. PR has been associated with altered neural responses related to learned dyspnea associations, which influence patients' perception of this symptom [63].

Education, self-management and behavior change may contribute to dyspnea relief by addressing its important affective component [51]. The development of self-management strategies to deal with dyspnea, the promotion of positive adaptative behaviors and the reduction of dyspnea-related affective stress during PR improves patients' emotional functioning and psychological outcomes [51,52,62]. Education on strategies such as sitting in a forward-lean position, adopt effective breathing techniques, like pursed lips breathing, and use a rollator to assist ambulation, seem to relieve dyspnea by i) optimizing the mechanical advantage and pressure-generating capacity of the inspiratory muscles, ii) reducing the respiratory rate and end expiratory lung volume, thus decreasing dynamic hyperinflation, and iii) facilitating the use of accessory muscles of respiration, minimizing reliance on the diaphragm during inspiration [50,52,64].

Inspiratory muscle training is an adjunct intervention with the potential to benefit selected patients with COPD who present inspiratory muscle weakness and dyspnea [45,65-67]. This is a subject under debate where controversial results have been found [66,68,69]. The larger randomized controlled trials in the field found no further improvements on dyspnea in patients performing inspiratory muscle training in addition to PR [68-71]. Contrarily, a recent smaller study with a longer duration of intervention, showed that in patients with severe COPD and inspiratory muscle weakness, the addition of inspiratory muscle training has the potential to further reduce dyspnea by reducing inspiratory neural drive [67].

3. Fatigue

Fatigue is the second most common and distressing symptom in patients with COPD [20,72] and is often overlooked by health care professionals. It is defined as "the subjective feeling of tiredness, exhaustion or lack of energy, that occurs on a daily basis" and prevents patients from performing their regular activities of daily life [8,73,74]. Fatigue is a multidimensional symptom that results from a complex interaction between physical, physiological, systemic and behavioral processes, poorly associated with the degree of airflow limitation [8,72,75]. The underlying causes and mechanisms responsible for fatigue in COPD are still unknown [8,17,20].

Recently, a model for fatigue in which hypoxemia and hypercapnia, as well as infectious COPD exacerbations and their treatment are precipitating factors for moderate to severe fatigue, has been proposed [8]. This model proposes that several systemic (e.g., low-grade systemic inflammation, exercise-induced oxidative stress, anemia), physical and psychological (e.g., dyspnea, physical deconditioning, lower limb muscle weakness, symptoms of anxiety and depression), and behavioral (e.g., physical inactivity, nocturnal awakening, low social support) factors are responsible for perpetuating fatigue in COPD [8]. A theoretical framework for fatigue in chronic respiratory diseases, not COPD-specific, in which the psychosocial state (e.g., mood, motivation, expectations), body homeostasis (e.g., oxygenation, metabolites, cardiovascular hemodynamic), peripheral factors (e.g., oxygen delivery, products of metabolism, global force capacity) and central factors (e.g., voluntary activation, motoneurons excitability) are responsible for fatigue development, with an important influence of dyspnea, physical deconditioning, anxiety, depression and cognitive failure, has also been published [76].

Independently of its origins, fatigue prevents patients with COPD from performing their regular activities of daily living, being associated with reduced physical activity levels, exercise intolerance and impaired functional status [8,17,20]. Specifically, leg fatigue is one of the main patients' complains and a major limiting factor for their exercise performance [77,78], being perceived as one of the main barriers to patients overall participation in activities [43].

Fatigue has been associated with frustration, worse mood status, dysfunctional illness believes and extreme limitations in social functioning, resulting in social isolation, feelings of loneliness and high mental burden, which affects patients' relationships and negatively impacts their emotional well-being, leading to symptoms of anxiety and depression and increasing the burden of the disease [8,79]. Patients mentioned to have lost joy in life due to fatigue, which further reinforces their demotivation to perform activities [79]. Fatigue is thus a key contributor to reduced health status and quality of life [8,20,79]. There is a known association between fatigue and poor sleep quality, higher frequency of exacerbations, increased risk of hospitalization, morbidity and mortality [8,17,21,80-82]. Optimization of pharmacological treatment seems to be insufficient to prevent further fatigue deterioration over time [83].

PR has shown to be effective for the management of fatigue in most – but not all – patients with COPD, but how different components of PR contribute to this benefit is not yet fully understood [60,75,82,84,85]. Changes in fatigue have been correlated with changes in some of its possible contributing factors, namely dyspnea, anxiety, depression and exercise tolerance, without the possibility to establish a causality relationship due to the study design [75]. Patients have reported the importance of exercise to reduce fatigue levels and social support to help coping with the mental burden of this symptom [79]. Education and self-management programs also allow patients to develop strategies on how to deal with fatigue and prevent its worsening, such as energy conservation and relaxation [17,79]. This emphasizes the need for personalized, comprehensive, interdisciplinary PR programs [75,79,82].

4. Cough and sputum

Approximately 23–87% of patients with COPD experience chronic cough and 32–75% sputum production, with 18–74% experiencing both symptoms [7,11-14,24,86].

Smoking and exposure to other noxious particles or gases results in airway inflammation, with releasing of inflammatory mediators and destruction of cilia [1,87]. Among these inflammatory mediators there are tussive agents and other mediators involved in cough reflex activation and mucus secretion, which lead to cough and sputum production [87]. Destruction of cilia impairs mucociliary clearance, further contributing to mucus hypersecretion and potential bacterial colonization, which per se stimulates cough and increases exacerbation frequency [88]. Hyperinflation, reduced peak expiratory flow, dynamic airway collapse and respiratory muscle weakness may negatively impact cough mechanics in patients with COPD, and together with altered sputum volume and viscosity, result in reduced cough effectiveness, further impairing the ability to clear secretions [89,90]. Bronchiectasis and gastroesophageal reflux – common comorbidities in these patients – are also often a cause of chronic cough [88,89,91], but the contributions of gastroesophageal reflux to cough and vice-versa in COPD requires further clarification [92].

Chronic cough and sputum secretion are independent risk factors for future exacerbations, which are important events in the management of COPD as they negatively impact hospitalization rates, health status and disease progression [1,14,23,24,89,90,93,94]. Chronic cough by itself, with or without sputum production, has been associated with poorer lung function, disease progression, more severe dyspnoea and healthcare utilization, and poorer quality of life in patients with COPD [11,14,23]. The impact of chronic sputum production by itself is less consistent, but it is suggested to be related with lung function decline, worse quality of life, increased risk of hospitalization and mortality (specially due to pulmonary infection) [90,95].

Patients with COPD may suffer from bouts of cough and difficult sputum expectoration which contribute to dyspnea [14,51]. Persistent cough and sputum production are related not only with feelings of shame and embarassing, worse mood, low self-esteem, symptoms of anxiety, depression and isolation, but also with poor sleep quality, higher levels of fatigue and impaired social and physical functioning, being a constant reminder of the disease [86,96]. Cough and sputum therefore result in high burden and impaired quality of life [14,23,86,90]. An association between these symptoms and urinary incontinence has been shown, which significantly affects patients emotional well-being and further limits social engagements [96]. Chronic cough and sputum production have been also associated with increased morbidity and mortality in COPD [23,86,88,90,93]. Patients have stated that alleviating their symptoms of cough and sputum could improve sleep quality and energy levels, and possibly reduce incontinence and social barriers, promoting a more normal life [96]. Identifying the presence or absence of chronic cough and increased sputum production in daily practice is important for the daily management of COPD.

Comprehensive interdisciplinary PR programs have shown to effectively decrease perceived symptoms of cough and sputum in patients with COPD [97-100]. Several proposed mechanisms are plausible. Exercise promotes airway clearance [101], which can be further enhanced by other therapies such as respiratory physiotherapy and breathing exercises using positive expiratory pressure devices [90]. A recent systematic review concluded that the active cycle of breathing techniques can improve sputum production and cough efficiency in patients with COPD [102]. Smoking cessation has also shown to improve cough and may enhance mucociliary function [87,90]. Education on symptoms management strategies and the emotional support given to patients throughout the sessions have the potential to alleviate cough and sputum, as well as their known consequences [96].

5. Anxiety and depression

Anxiety and depression are common comorbidities of COPD, if medically diagnosed, however, patients often report symptoms of anxiety and depression, through patients reported outcome measures, which has been the focus of this review. Patients with COPD are 85% more likely to develop symptoms of anxiety and have up to 55–69% increased risk of developing symptoms of depression compared to healthy individuals [103,104]. Several mechanisms may explain the development of these symptoms, which often coexist. The relationship between COPD and symptoms of anxiety/depression is likely bidirectional, i.e., COPD increases the risk of developing anxiety/depression and these symptoms also contribute to worse outcomes in COPD, such as increased risk of exacerbations or even death [103,104].

As described above, the anticipation of dyspnea triggers an emotional response of dyspnea-related fear, which is a mediator of anxiety and a contributor to an increased risk of depression [26,49,52,105]. The typical hyperventilation that occurs with symptoms of anxiety may increase gas trapping, resulting in increased dyspnea, which further contributes to the intensification and perpetuation of both anxiety and dyspnea [105,106]. Social isolation, low self-esteem, worse lung function, decreased physical activity levels, reduced exercise capacity, frequent exacerbations and hospitalizations are both contributing factors to anxiety and depression, and consequences of these symptoms, thereby leading to a vicious circle that perpetuates anxiety and depression [1,26,103,105-108]. These symptoms result in worse burden of respiratory symptoms, sleep disturbances, decreased cognitive function, reduced health status and impaired quality of life, contributing to the increased morbidity and mortality in COPD [1,26,103,104,108]. Anxious and depressive patients are also more likely to commit suicide [1]. Ensuring a good social and emotional support is fundamental to reduce symptoms of anxiety and depression [26].

PR, cognitive behavior therapy and mind-body interventions (e.g., yoga, relaxation) can play a role in the management of these symptoms [1,52]. A recent systematic review with meta-analysis showed that PR is an effective intervention to improve symptoms of anxiety and depression in COPD, with changes that exceed the established minimal clinically important difference [109]. These improvements are thought to occur as a consequence of exercise training – related improvements in dyspnea, exercise tolerance, health status and quality of life, which enhance performance of activities of daily living and social interactions [106,108,109]; combined with increased ability to manage dyspnea and stress, which is likely obtained through education and self-management [106,108].

Cognitive behavior therapy is a structured psychological intervention that combines cognitive psychotherapy with behavioral therapy [64]. It addresses the automatic thoughts and thinking patterns that contribute to symptoms of anxiety and depression, challenging patients' attitudes and beliefs, and promoting a change on their behavior and emotional state [26,64,105,106]. Although most studies have shown a positive effect of this therapy in reducing symptoms of anxiety and depression in patients with COPD [105,110], it appears that combining cognitive behavior therapy with standard PR does not result in additional benefits since there is a significant overlap between the content covered in this therapy and in the educational component of PR [110].

Relaxation therapies, such as breathing techniques, sequential muscle relaxation, yoga and mindfulness meditation, aim to reduce anxiety-related physiologic changes and may have potential benefits on symptoms of anxiety, depression and dyspnea, however scientific evidence is yet scarce [26,105].

6. Pain

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [111] and affects 32–85% of patients with COPD [18,19]. These patients report around 2.6 times greater pain severity and 3.7 times more pain interference on daily activities than age- and gender-match healthy controls [112]. Pain of moderate intensity [18,19,30,113] that affects the head, neck, chest, shoulders, upper limbs, trunk, hips and knees has been usually reported [19,30,113,114]. Little is known regarding the type of pain and its etiology in these patients [18,19,30,115].

There are several complex factors that may contribute to the higher prevalence of pain in COPD. The systemic inflammatory process inherent to COPD activates proinflammatory cytokines that contribute to the generation of pain and lower the threshold to painful stimuli [19,112]. The typical hyperinflation that occurs in these patients puts thoracic articulations in an hyperextended position and decreases their range of motion, leading to ligamentous strain, excessive joint force, postural dysfunction and mechanical limitation of chest wall movement, which possible contributes to thoracic pain [112,116]. Hyperinflation also results in mechanical disadvantage of the inspiratory muscles, which makes these muscles more prone to overuse injuries and delayed onset muscle soreness [112]. Some common musculoskeletal disorders and comorbidities in COPD, such as compression fractures, vertebral deformation, costovertebral arthropathy, osteoporosis and osteoarthritis, are other potential causes of pain [19,30,112,114]. Cough may also trigger or aggravate pain in patients with COPD [117]. Since pain and dyspnea activate common areas of the brain, due to the similar sensory and affective-related brain networks, the prolonged experience of dyspnea and related activation of brain centers in patients with COPD may induce permanent changes in pain perception [112].

Patients have reported a significant negative impact of pain on their daily lives [30]. Pain has been associated with increased symptoms of dyspnea, fatigue, anxiety and depression, decreased physical activity levels and exercise capacity, impaired performance of activities of daily living, sleep disturbances, worse mood, frustration and less enjoyment of life, all of these contributing to social isolation, worse quality of life and poorer clinical outcomes [16,18,19,30,112,113,115,116,118-120]. These negative consequences of pain may lead to pain-related fear of movement, particularly in relation to pain-exacerbating activities, which results in avoidance of physical activity and leads to a downward spiral of increased disability [112].

Despite the prevalence and impact of pain in COPD, information regarding pain management is scarce in COPD guidelines [16]. The impact of an effective pain management intervention in patients with COPD is also unknown [115]. In a recent qualitative study, patients with COPD identified PR as an appropriate setting for pain management and emphasized the importance of pain education [114]. In the same study, health professionals reported that the improvements in muscle strength and sense of control achieved with PR diminished the impact of pain [114]. Nevertheless, studies assessing the role of PR on pain in these patients have shown no effect of the intervention [19,121], i.e., PR neither aggravates nor reduces pain intensity or its interference with daily activities [121]. Treatment approaches addressing the emotional and psychological component of pain, which consider the interactive relationship between experiences of pain, dyspnea and anxiety, and also establishing pain coping strategies might be helpful in patients with COPD [112,114,120]. In the absence of specific recommendations for COPD, it has been shown that multimodal approaches including physical activity, cognitive behavioral therapy and self-management education are the most effective for the management of chronic pain [122].

7. Sleep disturbances

Sleep represents around one third of the average lifetime and plays a crucial role on physical and mental health [123]. It is divided in two stages – non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep – that alternate in a cyclic manner [124]. Patients with COPD often suffer from sleep disturbances and poor sleep quality, with a prevalence ranging from 36–85.3%, which have been considered important in the monitoring of disease progression [1,31,32]. These sleep disturbances lead to complains of insomnia, increased sleep latency, non-restorative sleep, altered sleep architecture, reduced total and REM sleep time, frequent changes in sleep stages, arousals and daytime sleepiness [31,37,125-131].

There are several mechanisms contributing to sleep disturbances in patients with COPD. During normal sleep there is a reduction in ventilatory drive and chemoreceptor sensitivity, leading to decreased tidal volume, increased upper airway resistance and altered ventilatory responses to hypoxemia and hypercapnia [123,125]. There is also an active inhibition of skeletal muscles (including the accessory muscles of respiration) during REM sleep and changes in functional residual capacity and ventilation-perfusion relationship [125]. Although these physiological changes have no impact in healthy individuals, in patients with COPD who already suffer from airflow obstruction, hyperinflation and diminished efficacy of diaphragmatic contraction, the associated decrease in minute ventilation and hypoventilation may lead to hypoxia, hypercapnia and increased work of breathing, contributing to arousals and sleep disturbances [29,31,123,125,126]. The typical symptoms usually experienced by patients with COPD during the night and/or early morning, such as dyspnea, cough, wheezing and sputum, also contribute to difficulties in initiating and maintaining sleep [28,29,31,37,126]. Some medication usually prescribed may also contribute to sleep disturbances [27,123]. Obstructive sleep apnea, a common comorbidity in patients with COPD, further contributes to poor sleep quality [31,123]. Symptoms of anxiety and depression may precipitate or worsen insomnia [27].

Independently of the etiology, patients with poor sleep quality and sleep disturbances present reduced physical activity and exercise capacity, lower daytime energy, more fatigue, impaired daily activities, higher levels of depression, poor control of the disease, increase levels of respiratory symptoms and reductions in lung function [29,31,37,126,132]. It may also lead to impaired memory and cognition [37]. Sleep disruption and fragmentation results in enhanced systemic inflammation and impaired immune function, increasing the risk of exacerbations [29,31,37]. Ultimately, sleep disturbances result in worse health status, decreased quality of life and reduced survival [29,37,125-127,132].

Cognitive behavioral therapy for insomnia, which includes stimulus control, sleep restriction, sleep hygiene, training in relaxation and cognitive therapy, has positive results on subjective sleep measures in patients with COPD [133]. Progressive muscle relaxation exercise technique, which involves the voluntary stretching and relaxation of large muscle groups gradually from the hands to feet, also showed positive results in improving subjective sleep quality in these patients [134,135]. Nevertheless, to the authors' best knowledge, studies assessing the role of these interventions on sleep quality of patients with COPD using objective measures are lacking.

PR has been hypothesized as an effective intervention to improve sleep quality in patients with COPD since it i) contributes to muscle adaptations that result in increased respiratory muscle strength, ii) improves systemic inflammation, iii) increases energy consumption and endorphin secretion, iv) increases physical fitness and physical activity, and v) decreases symptoms of anxiety and depression [32,136]. Nevertheless, studies assessing the role of PR on sleep quality have shown controversial results, with some studies reporting that PR improved subjective sleep quality [32,136-138] and others finding no improvements in either subjective [139,140] nor objective (i.e., polysomnography, actigraphy) [140-142] sleep measures.

8. Cognitive decline

Cognition refers to any intellectual process that enables an individual to perceive, register, store, retrieve and use information/knowledge to adapt the behavior to new situations, change preferences and function in the surrounding environment [143,144]. Around 25% of patients with COPD complain of perceived memory deficits and related confusion [34], and 10–57% suffer from some cognitive impairment [144,145]. Patterns of impairment in patients with COPD are diffuse, involving domains like attention, executive functioning, (visual) memory and reproduction, problem-solving, concentration, logical and abstract reasoning, planning, coordination and organization [144]. Several mechanisms, such as hypoxemia, hypercapnia, inflammation, smoking, reduced physical activity, comorbidities (e.g., depression, sleep disturbances and vascular disease), exacerbations and dietary insufficiencies, have been proposed as potentially contributors to symptoms of cognitive decline in COPD [40,144]. More recently, the role of dyspnea as a cause of cognitive impairment (not specifically in COPD) has been pointed out, as this symptom activates brain networks that are also involved in cognitive, affective and motor processing, limiting the available brain processing capacities for this simultaneous performance [38]. It is likely that the combination and interaction among the different mechanisms, rather than a single mechanism, explains the development of cognitive impairment [40,144].

Cognitive decline results in memory and concentration problems; decreased ability to comprehend long, detailed and fast instructions without losing attention; inability to transfer previous knowledge to new events; difficulties in handling new situations; problems in choosing appropriate behavioral responses; difficulties in flexible thinking and in initiating activities [39]. It affects executive function which involves skills such as planning, organization, behavioral initiation and motivation, impairing patients' ability to perform activities of daily living and self-management skills [39,146]. Patients have reported impaired memory, concentration and planning as barriers to their participation in daily and social activities [43]. Cognitive decline has been associated with increased disability, poor adherence to treatment, worse health outcomes, higher risk of exacerbations and hospitalization for respiratory problems, longer hospital stays and mortality [39,40,146]. Few studies have explored the trajectories of change in cognitive function in patients with COPD, but it appears that older age, lower educational levels and reduced 6-minute walk distance are predictors of worsening cognitive function [147]. Since exercise capacity is a modifiable risk factor of cognitive decline, PR has been proposed as a treatment to improve cognitive function in COPD [40,143].

Exercise training has positive short-term effects on cognition, namely long-term memory, verbal fluency, attentional capacity, apraxia and reasoning skills, which can occur through several pathways [143,144,148,149]. First, it potentiates the release of several hormones, such as noradrenalin, serotonin and ß-endorphin, which mediate positive effects on psychological well-being, improve mood and may act as physiological modulators to memory [148]. Second, it changes the levels of neurotransmitters (e.g., acetylcholine, dopamine) in the central nervous system that are able to promote cognitive function [148]. Third, it increases cerebral blood flow and possibly oxygenation [144,148]. It also increases cerebral growth factors, which are involved in the rate of differentiation/apoptosis of cerebral cells and hippocampal neurogenesis, possibly increasing hippocampus volume and positively influencing memory [144,148]. Lastly, exercise improves exercise capacity and coordinative ability, contributing to increased ability to perform activities of daily living [40,148]. All these mechanisms seem to have positive effects on cognitive function. PR also provides social engagement and support, and reduces symptoms of anxiety and depression, favorable effects that can be promising in patients with cognitive impairment [143].

Given the deleterious effects of dietary deficiencies and smoking on cognition, nutritional support and smoking cessation have shown beneficial effects on cognitive function in the general population, but studies in COPD are missing [143,144]. Cognitive training demonstrated to improve cognitive functioning in healthy elderly and people with mild cognitive impairment, but studies in COPD are scarce with one randomized controlled trial showing no additional benefit [144,150]. Given that cognitive impairment affects patients' memory and ability to change behavior, health professionals may adapt interventions to overcome these barriers by identifying support systems and tailoring PR programs to patients' individual capacity (e.g., involving carers, providing visual cues and written information) [146].

7. Summary

Several respiratory and non-respiratory symptoms affect the daily life of patients with COPD, independently of the severity of their disease, and contribute to the decreased health status and impaired quality of life of these patients. Symptoms may have different geneses and result in various physical, emotional and social manifestations; although some of the underlying mechanisms are not yet fully understood. Some of these symptoms can be both a consequence and a contributing factor to other symptoms, leading to a vicious circle that increases and perpetuates symptom burden. To effectively tackle symptoms complexity, comprehensive, tailored and interdisciplinary PR programs are needed.

PR programs act through different pathways, such as optimizing the function of different systems in the body, promoting positive adaptative behaviors or addressing the disease affective component, which involves the integration of several therapies (e.g., exercise training, education, self-management, behavior change, respiratory physiotherapy, smoking cessation, relaxation, nutritional support, inspiratory muscle training). Interdisciplinary programs require interdisciplinary teams, thus a team including physicians, physiotherapists, respiratory therapists, exercise physiologists, nurses, psychologists, behavioral specialists, nutritionists, occupational therapists and social workers must be available, and its contribution to the overall perceived benefit of PR has been recognized by patients [45,151,152].

8. Expert opinion

There is increasing awareness, since the end of the 90s, that chronic respiratory disease does not only affect the lungs and integrity of breathing, but also has a multitude of extra-pulmonary consequences, including physical, psychosocial and behavioral impairments [2-5]. Pharmacological treatment has only limited power to tackle these consequences and thus patients' condition continues to deteriorate over time [44]. PR is now accepted as a powerful intervention to comprehensively target extra-pulmonary consequences of COPD using a multi-faceted and interdisciplinary team approach [45,48,60]. Traditionally, when discussing extra-pulmonary consequences, studies tend to focus more on physiological measures, such as exercise capacity, and quality of life to investigate the effectiveness of PR and assess whether an individual shows a significant response to the intervention [151,153-156]. Based on current insights, it is proposed to investigate the multidimensional response to PR, including symptoms perception and social and emotional functioning [154,157].

Patients consider symptomatic relief and its impact on their daily life as one of the most important aspects of disease management [158-160]. Assessment of symptoms is likely to be the closest we can get to the core of the disease burden in our patients [161]. Yet, currently little attention is given to symptom assessment beyond dyspnea. In 2014, a survey amongst 430 centers from 40 different countries, revealed that dyspnea was assessed in about 40% of centers, while no other symptom was assessed in more than 10% of centers [151]. Moreover, national guidelines mainly emphasize the importance of assessing dyspnea and quality of life [155,156]. We want to highlight the importance to consider a range of symptoms – not only dyspnea, but also fatigue, cough, sputum, anxiety, depression, pain, sleep disturbances and cognitive decline – as part of a core outcome set for PR.

We foresee that – in five years from now – one or more initiatives will be taken to propose a core outcome set for PR. This will be an important step towards quality improvement in PR centers worldwide, as it will highlight the minimal assessment procedures that are needed to ensure a multidimensional patient assessment and facilitate comparisons and interpretations of results obtained [162-164]. In order to optimize the adoption of such approach, it is crucial that this core outcome set can be translated to centers with low resources.

We appreciate that frequently used composite measures assessing impact of the disease or quality of life – e.g. COPD Assessment Test, Saint George Respiratory Questionnaire, Chronic Respiratory Diseases questionnaire – oftentimes address several of the proposed aspects, but generally only a summary score is taken into account by clinicians and researchers. Many measures with known and unknown measurement properties have been used to assess the same outcome, which limits recommendations about the most suitable tools to assess symptoms in COPD [10]. A comprehensive review on symptoms, respective tools and measurement properties might constitute an important first step for this discussion. But other steps would be equally important as integrating the views of patients, loved ones and policy makers in this discussion of which symptoms to assess and which tools to use, and reach a consensus; hold face to face meetings to finalize the recommendations, and report it according to guidance [165,166].

9. Key issues

- More than 80% of patients with COPD suffer from symptoms burden on a daily basis
- Dyspnea, fatigue, cough, sputum, anxiety, depression, pain, sleep disturbances and cognitive decline are highly prevalent symptoms in patients with COPD
- Symptoms result in several non-pulmonary manifestations and play a crucial role on reduced health status and impaired quality of life
- A thorough symptoms assessment (beyond dyspnea) should be routinely performed
- Comprehensive symptoms assessment allows identification of treatable traits, tailoring of interventions and assessment of their real-life impact
- An effective symptoms' management demands comprehensive, tailored and interdisciplinary PR programs involving the integration of several therapies (e.g., exercise training, education, self-management, behavior change, respiratory physiotherapy, smoking cessation, relaxation, nutritional support, inspiratory muscle training)
- To deliver an optimal interdisciplinary PR program, an interdisciplinary team must be available

10. References

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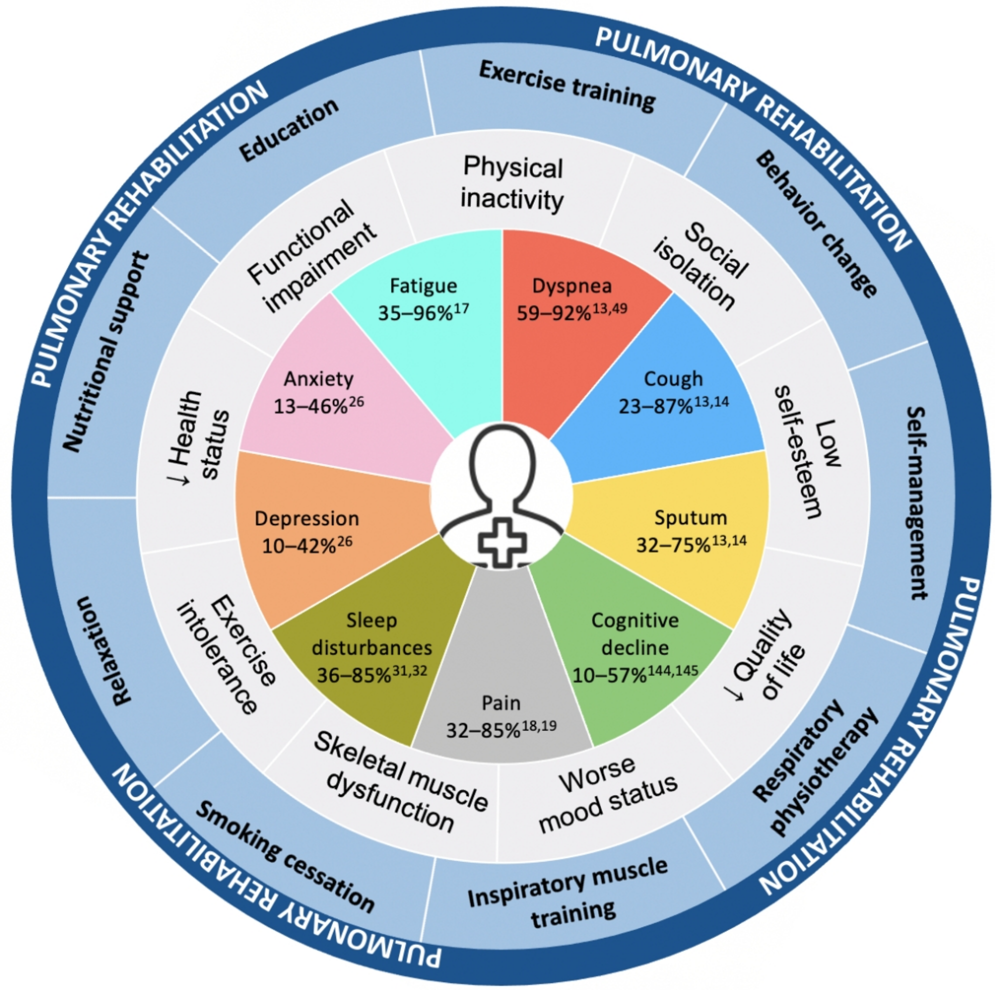
List of Figure Legends

Figure 1. Overview of symptoms prevalence, known extra-pulmonary precipitating and perpetuating factors, and targeted interventions to tackle symptoms burden and consequences within an interdisciplinary pulmonary rehabilitation framework.



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