Helping COPD patients change health behavior in order to improve their quality of life

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Abstract: Chronic obstructive pulmonary disease (COPD) is one of the most prevalent and debilitating diseases in adults worldwide and is associated with a deleterious effect on the quality of life of affected patients. Although it remains one of the leading causes of global mortality, the prognosis seems to have improved in recent years. Even so, the number of patients with COPD and multiple comorbidities has risen, hindering their management and highlighting the need for futures changes in the model of care. Together with standard medical treatment and therapy adherence – essential to optimizing disease control – several nonpharmacological therapies have proven useful in the management of these patients, improving their health-related quality of life (HRQoL) regardless of lung function parameters. Among these are improved diagnosis and treatment of comorbidities, prevention of COPD exacerbations, and greater attention to physical disability related to hospitalization. Pulmonary rehabilitation reduces symptoms, optimizes functional status, improves activity and daily function, and restores the highest level of independent physical function in these patients, thereby improving HRQoL even more than pharmacological treatment. Greater physical activity is significantly correlated with improvement of dyspnea, HRQoL, and mobility, along with a decrease in the loss of lung function. Nutritional support in malnourished COPD patients improves exercise capacity, while smoking cessation slows disease progression and increases HRQoL. Other treatments such as psychological and behavioral therapies have proven useful in the treatment of depression and anxiety, both of which are frequent in these patients. More recently, telehealthcare has been associated with improved quality of life and a reduction in exacerbations in some patients. A more multidisciplinary approach and individualization of interventions will be essential in the near future.

Keywords: COPD, health related quality of life, comorbidity, disability, pulmonary rehabilitation, telehealthcare

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent and debilitating diseases in adults worldwide. According to the estimation of the World Health Organization, 210 million people have COPD and 3 million people died of COPD in 2005. COPD is associated with high morbidity and mortality and with a significant deterioration in the quality of life (QoL), especially, but not only, in the advanced stages of the disease.

Fortunately, several recent studies suggest a decrease in the global impact of the disease. The latest estimations of the Global Burden of Disease Study show that COPD was, in 2010, the third-leading cause of mortality worldwide and ninth in the combination of years of life lost or lived with disability (disability-adjusted life...
years, or DALYs). These data represent an improvement over previous predictions made by the same group and indicate that global mortality and DALYs for COPD in all ages have decreased between 1990 and 2010 by 6.4% and 2.0%, respectively (or measured in age-standardized death rates, a reduction in mortality of 43% and in DALYs of 25%). Two other studies performed with large databases or cohorts also suggest that the prognosis of patients with COPD has improved in the last decade. Because COPD, like many other medical conditions, is not presently curable, the most likely future scenario is that most COPD patients will live progressively longer and thus will suffer more often from concomitant chronic diseases. In this sense, several studies performed in patients hospitalized for COPD have reported an increase in the percentage of people older than 85 years of age, along with a greater prevalence of comorbidities and a decrease in physical performance.

This should lead physicians and other health players to expand the traditional assessment of chronic diseases (based on terms of diagnosis and morbidity and mortality rates) to include other priorities, such as preventing disability, preserving quality of life, and integrating patient perception and adaptation into the limitations caused by the disease (Figure 1).

In the present narrative review, we will highlight the recent literature in order to evaluate nonpharmacological therapies focused on preserving the QoL of patients with COPD and the desirable changes in the care model for management of patients with COPD and several concomitant chronic diseases, overcoming the single-disease focus that pervades medicine.

**Search strategies**

We performed multiple searches in PubMed and the Cochrane Library about the different nonpharmacological measures that have been related to QoL in patients with COPD. We also used various search strategies that combined the keyword “COPD” with other terms, such as “comorbidity”, “depression”, “pulmonary rehabilitation”, “disability”, and “telehealthcare”, among others. We selected the most relevant and recent articles, prioritizing systematic reviews and meta-analyses.

**Quality of life and health-related quality of life**

In medicine we often use the terms QoL and health-related quality of life (HRQoL) as synonyms, when in fact they are two different concepts. QoL is a totally subjective and individual notion based on personal perception, culture, and values. By contrast, HRQoL is defined as the extent to which one’s usual or expected physical, emotional, and social well-being are affected by a medical condition or its...
treatment, and this can be measured with questionnaires that provide a standardized method for quantifying the impact of disease and enable assessment of the changes produced by the different interventions and disease progression. Concepts of comorbidities and multimorbidity have been complex and time-consuming, limiting their utility in clinical practice. This difficulty has been remedied by the recently validated COPD Assessment Test (CAT). CAT is included in the new Global initiative for chronic Obstructive Lung Disease normative alternatively to dyspnea, measured with the modified Medical Research Council scale, to assess symptom severity in the combined scale. However, to our knowledge, CAT has not been validated for mortality, and the cutoffs used (ten) were selected arbitrarily.

Generic questionnaires allow comparison of HRQoL among different diseases and may be more useful in patients with COPD and multimorbidity. In contrast, disease-specific questionnaires are more useful in assessing responsiveness and clinical changes in the evolution of COPD and the impact of interventions (Table 1). Both methods have strengths and weaknesses and perhaps they are complementary. Unfortunately, the use of COPD-specific questionnaires has been complex and time-consuming, limiting their utility in clinical practice. This difficulty has been remedied by the recently validated COPD Assessment Test (CAT). CAT has shown an excellent correlation with the Saint George’s Respiratory Questionnaire (SGRQ) and good sensitivity in detecting changes in the disease, such as exacerbations and improvement with rehabilitation.

HRQoL questionnaires overcome the misconception that only lung-function values are trustworthy to evaluate the impact, prognosis, and evolution of COPD. It is well known that spirometric values are only moderately related to HRQoL, whereas dyspnea, depression, exacerbations, comorbidities, anxiety, and exercise tolerance show a more consistent association. Results for age and gender are controversial.

Comorbidity and multimorbidity

Adults with multiple chronic conditions are the main users of health care services and account for more than two thirds of health care spending. These patients had lower physical function – greater frailty and risk of disability – and a decrease in HRQoL even after adjustment for confounding variables such as age, sex, education, and perceived social support.

The importance of comorbidities in COPD patients and their prognostic implications have been increasingly recognized in the last decade. Heart disease, hypertension, musculoskeletal disorders, and diabetes, among many other diseases, are common in COPD patients, and several epidemiological studies have shown that lung function impairment is associated with an increased risk of comorbid diseases. In fact, many patients with COPD have multiple concurrent comorbidities, and hence the term “multimorbidity” would be more accurate. Although multimorbidity is sometimes used interchangeably with comorbidity and pluripathology, multimorbidity implies a different concept. Comorbidity technically indicates a condition or conditions that coexist in the context of a principal disease, in our case COPD, whereas multimorbidity refers to co-occurrence of two or more chronic medical conditions that may or may not directly interact with each other within the same individual.

The complexity of managing several chronic diseases simultaneously in the same patient requires changes in health care delivery.

In a recent study performed in Scotland, multimorbidity was present in 23% of the 1.75 million people included in a database from >300 medical practices. In this study, only 18% of patients had COPD as an isolated disease, whereas almost half had three or more concomitant disorders. Similarly, in a cohort study conducted in patients with moderate or severe COPD (mean forced expiratory volume in 1 second of 51%), 62% of patients had three or more comorbidities and only 2% had COPD exclusively. This is the reason why some authors consider COPD to be just one component – and not necessarily the most important one – of the multimorbidity complex in many patients. Several reports have highlighted the relationship between comorbidities and an impairment of HRQoL in COPD. Two studies performed with a generic questionnaire (short-form

![Figure 2](https://example.com/image2.png)

**Figure 2** Health-related quality of life.
health survey (SF-36) showed that the combination of cardiac and respiratory disorders had a negative synergistic effect on HRQoL and that COPD patients with comorbidity had impaired scores in all domains when compared with COPD patients without comorbidity. Other publications also showed significant relationships between comorbidity and disability and poorer scores in the SGRQ and an inverse relationship between depression, heart failure, and ischemic heart disease and HRQoL measured with SGRQ.

<table>
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<th>Table 1 Examples of several HRQoL questionnaires in COPD</th>
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Notes: *A shorter 40-item version (SGRQ-C) has been validated specifically for COPD patients. **A modified self-administered version exists.

Abbreviations: SIP, Sickness Impact Profile; SF-36, Medical Outcome Study, Short Form; NHP, Nottingham Impact Profile; SGRQ, Saint George’s Respiratory Questionnaire; CRQ, Chronic Respiratory Disease Questionnaire; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life.

Figure 3 Differences in evaluation between comorbidity and multimorbidity.

Note: The figure on the left represents the concept of comorbidity; the figure on the right represents the concept of multimorbidity.

Abbreviation: COPD, chronic obstructive pulmonary disease.
Unfortunately, the information about how to organize continuous care of these patients is limited.37,38 Expert consensus suggests avoiding fragmentation of care with multiple specialists involved, each attending his or her own pathology. From the perspective of the health service, treatment of diseases in isolation is inefficient, leading to duplication of care. For patients, repeat requests to attend different clinics for each chronic disease are inconvenient and confusing.12 It is necessary to identify which clinician should have the primary responsibility for helping patients make decisions and to prioritize a multidisciplinary approach in collaboration with nurses, social workers, and physiotherapists, among others. When COPD is the most important patient health problem, a respiratory specialist may be the optimal primary decision maker, although these specialists should be trained in the management of the most frequent comorbidities. In other patients, oversight by a generalist, in conjunction with targeted assistance from specialists with expertise and experience in caring for complex patients with multiple chronic conditions, may be the best way to supervise the care team, as this requires integrating across all conditions within the context of each patient’s health goals and priorities. For these patients, in addition to providing the best treatment possible for their diseases, it is essential to optimize their physical function, ascertaining patient-important outcomes and avoiding inappropriate, nonbeneficial care.22 Of note, these patients are usually excluded in clinical trials, so that the scientific evidence about interventions is in many cases scanty. However, many of the interventions that we will discuss below can be particularly useful in this subgroup of patients: pulmonary rehabilitation remains useful, although the improvement in exercise tolerance and QoL may be smaller in patients with musculoskeletal disorders or disability outcomes.39 Physical therapies have proved beneficial even in frail, institutionalized older patients.40,41

Nonpharmacological treatments that improve the HRQoL in COPD

Exacerbation prevention

Exacerbations of COPD are related to an increase in short-term and long-term mortality, decline in lung function, and worsening of HRQoL. Furthermore, it is one of the events most feared by patients, so prevention is a cornerstone in the management of the disease.19,26,42,43

Diverse pharmacological therapies have proved useful in reducing the number of exacerbations and hospital admissions.44 Additionally, other interventions, such as patient education for self-management, hospital at home for selected patients, discharge planning from hospital to home, and exercise prescription during hospital stay have demonstrated benefits in patients hospitalized for COPD.45–49 Pulmonary rehabilitation in stable patients showed a reduction in admissions for related respiratory illness, alongside a 50% reduction in the length of stay whenever hospitalization was required and a reduction in the number of exacerbations.50,51 Different strategies for disease management have shown a 40% reduction in COPD hospitalizations and a similar reduction in consultations at the emergency department, although not all studies have shown similar results, probably because of differences between programs.52–54 A Cochrane review concluded that pulmonary rehabilitation initiated during hospitalization for COPD exacerbation or shortly after discharge significantly reduced the likelihood of rehospitalization (odds ratio = 0.22; 95% confidence interval [CI] = 0.08–0.58), with a number needed to treat of 4 (95% CI = 3–8) and a reduction in mortality (odds ratio = 0.28; 95% CI = 0.10–0.84) with a number needed to treat of 6 (95% CI = 5–30). The group in the rehabilitation program also improved in HRQoL (measured with the fatigue and dyspnea domains of the Chronic Respiratory Questionnaire) and in the total scale and the activity and impact subscales of the SGRQ, although not in the symptoms.55 These results were replicated in other meta-analyses, with a moderate quality of evidence and strong recommendation in favor of the intervention.56,57

Prevention of disability

One of the main goals in managing patients with severe COPD is to prevent adverse events related to exacerbations and hospitalizations, especially the loss of functional capacity and subsequent physical dependence in basic and instrumental activities of daily living.58 New onset of disability as part of hospitalization is common; at least 30% of patients older than 70 years of age and hospitalized for a medical illness are discharged with a new disability related to activities of daily living.59 Post-hospital disability has a major effect on the QoL and independence of chronic patients and on health-related expenditures, in what some authors recently termed “post-hospital syndrome.”60 During hospitalization, most patients spend the majority of time in bed and nutritional status often deteriorates, accelerating muscle wasting.61 In COPD, disability is related to lower levels of well-being and health status, increased levels of distress, depression, and a more pronounced illness perception.62 Hospitalization for acute exacerbation of COPD causes marked inactivity and a loss of muscle strength, reaching an average of 5% in quadriceps, that is not fully recovered after 90 days.63
Early mobilization and early rehabilitation may reduce the incidence of hospitalization-associated disability.2,6,14 Particular attention should be focused on avoiding hospital processes that are not essential and that can impair functional recovery – ie, prolonged bed rest, inadequate nutritional support, overly restrictive diets, overuse of monitors, urinary catheters, and intravenous lines that tether patients, and the use of sedating medications – as all may contribute to loss of physical function.

Management of depression and anxiety
Depression is common in COPD patients, with an estimated prevalence of 25% – nearly two times higher than people without COPD. This prevalence increases to 57% in patients with severe COPD, of whom 18% have major depression and only 6% receive treatment.65 The prevalence of anxiety in patients with COPD is also high, and the two conditions frequently occur concurrently in the same patient. Generalized anxiety disorders can occur in 10%–33% of patients with COPD, and the prevalence of disorders and panic attacks ranges from 8%–67%.66 Untreated depressive symptoms are associated with a decrease in adherence to medical treatment and pulmonary rehabilitation, lower exercise capacity, higher mortality and hospital readmissions, and substantial impairments in psychological, physical, and social functioning, along with a worsening of HRQoL.67–69 In a recent meta-analysis, comorbid depression or anxiety increased the risk of mortality in COPD patients (depression relative risk = 1.83; 95% CI = 1.00–3.36), (anxiety relative risk = 1.27; 95% CI = 1.02–1.58) and increased the risk of COPD exacerbation by 31%.70 In addition to pharmacological treatment, several nonpharmacological therapies such as pulmonary rehabilitation, psychotherapy, educational sessions, relaxation therapy, and group cognitive behavioral therapy can improve depression scores.71–75 A systematic review showed that psychological interventions and lifestyle interventions that include an exercise component significantly improve symptoms of depression and anxiety by 28% and 23%, respectively, in people with COPD. The best results were observed with programs based on multicomponent exercise training, with a decrease in depression and anxiety symptoms of 47% and 45%, respectively.76

Improvement of physical activity
Patients with COPD have lower levels of physical activity than the general population. In COPD patients, greater physical activity correlated significantly with improvement in dyspnea, HRQoL, and mobility.77 However, a moderate relationship exists between daily physical activity and exercise capacity, suggesting that exercise interventions need to target not only exercise capacity but also behavioral changes with regard to daily physical activity, in order to achieve improvement in both parameters. Additionally, the increased exercise capacity achieved with pulmonary rehabilitation may not be accompanied by increased daily physical activity.78

Several studies have evaluated the beneficial role of physical activity in the prognosis and evolution of COPD. In one cohort study with 11 years of follow-up, smokers with moderate or high levels of exercise had lower risk for developing COPD than did smokers with low levels of exercise. In addition, this study showed that a higher level of physical activity decreased the loss of lung function, both in smokers and in former smokers.79

Reduction in physical activity is a well-known consequence of COPD, but inactivity is itself a cause that contributes to the greater loss of pulmonary function, so that smokers with low levels of physical activity are more likely to develop COPD. Physical exercise lowers oxidative stress, has an anti-inflammatory effect, and reduces the frequency of respiratory tract infections, providing a number of mechanisms that could mitigate the harmful effects of smoking.80

The results of a recent study in primary care in Spain demonstrated that individual counseling is effective in increasing physical activity in inactive people. The effect is small but significant in terms of public health at the population level.81 This effect is greater in patients with chronic diseases. Furthermore, there is evidence indicating that physical exercise helps smokers to quit smoking.82 Additionally, daily walking intensity is related to HRQoL, as measured with a generic questionnaire (SF-36) and a specific questionnaire for COPD (SGRQ), and to decreased biomarkers related to cardiac distress in stable COPD patients.83

Prevention of malnutrition
Disease-related malnutrition is a common problem in individuals with COPD, with 30%–60% of inpatients and 10%–45% of outpatients said to be at risk.84 Malnourished COPD patients demonstrate greater gas trapping, lower diffusing capacity, and a reduced exercise performance when compared with heavier, nonmalnourished patients with a similar severity of disease.85 The relationship between malnutrition and COPD is not completely elucidated; malnutrition may be the consequence of greater disease severity, but it may also be a factor in the wasting of peripheral and respiratory muscles involved in breathing or the impairment of
the immunological system, accelerating COPD progression. Interestingly, in chronic anorexia nervosa, the loss of body weight is accompanied by a loss of lung tissue, mimicking emphysematous-like changes.86

Assessment of the patient’s nutritional status becomes a necessity for early detection of increased risk for malnutrition and establishes the degree of nutritional support to apply. In a recent systematic review, nutritional support was not associated with improvement in forced expiratory volume in 1 second, although it showed a significant increase in maximal inspiratory and expiratory capacity and sternomastoid and quadriceps strength, and a reduction in fatigability.87 Other studies have shown improvement in HRQoL and well-being in malnourished COPD subjects who received nutritional support.88 Finally, another systematic review from the Cochrane collaboration showed improvement in the distance covered in the 6-minute walking test (39.96 m; 95% CI = 22.66–57.26 m).89 In contrast, for other COPD patients, obesity is an important and increasing problem that limits exercise capacity, producing restriction and aggravating respiratory dyspnea.90

Smoking cessation
Smoking is a major risk factor for developing COPD, and smoking cessation is a priority in the management of the disease. Despite clear evidence linking smoking with morbidity and mortality in COPD, a third or more of patients with moderate and severe COPD continue to smoke.91 Smoking COPD patients have a lower HRQoL than nonsmokers and a higher prevalence of depressive symptoms, even in the same respiratory disease category and severity grade.92 Smoking cessation has been related to HRQoL improvement.93 In COPD patients, intensive counseling and pharmacotherapy resulted in comparable results for individuals who stopped smoking and the general population.94

Self-management programs
Self-management programs are defined as “any formalized patient education programme aimed at teaching skills needed to carry out medical regimens specific to the disease, guide health behavior change, and provide emotional support for patients to control their disease and live functional lives.”95 These programs aim to develop patients’ coping skills to maintain as active a lifestyle as possible, promote correct use of drugs, and encourage the early identification of increasing symptoms heralding an exacerbation so that they can be treated early. In a meta-analysis, self-management improved HRQoL measured with SGRQ but did not reach a clinically relevant improvement of four points.96 Self-management is also related to the use of less rescue medication, reduction in unscheduled doctor and nurse visits, and a possible reduction in hospitalizations for COPD exacerbation.97 In a recent study, self-management did not decrease hospital admissions in the overall study population, although only 42% of the intervention groups were classified as successful self-managers at the end of the study period on the basis of their recognition and appropriate use of treatment. Interestingly, this subgroup of successful self-managers had a significantly reduced risk for readmission or death. Younger patients and those not living alone are more likely to correctly use self-management techniques and derive benefit from them.96 More recently, a self-management intervention based on behavioral changes in patients and health care providers with an emphasis on motivational interviewing and a greater alliance between patient and interventionist showed promising results, with improvements in QoL and patient acceptability.97

Pulmonary rehabilitation
Pulmonary rehabilitation is a broad therapeutic concept that includes conditioning, breathing retraining, education, and psychological support, and it comprises lower- and upper-extremities exercise, ventilatory-muscle training, education to improve medication compliance, smoking cessation, nutrition, exercise, psychological support, and health preservation. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, improve activity and daily function, and restore the highest level of independent physical function in patients with COPD by stabilizing or reversing systemic manifestations of the disease.98 Several studies and meta-analyses have shown that pulmonary rehabilitation improves HRQoL more than pharmacological treatment does. This improvement is observed even in the absence of clinically significant improvements in exercise. A Cochrane meta-analysis of 31 randomized controlled trials, 13 of which measured QoL, indicated that HRQoL measured with the Chronic Respiratory Questionnaire or the SGRQ improved and exceeded the minimal clinically important difference with pulmonary rehabilitation.99

Increase in medication adherence
Access to drugs alone is not sufficient to control chronic conditions. According to the World Health Organization, adherence to long-term therapy for chronic illnesses in developed countries averages 50%.100 It is undeniable that
many patients experience difficulty in following treatment recommendations. In a recent study, 18% of the respiratory patients interviewed quit the therapy spontaneously; the first cause of this discontinuation was the complexity of treatment, even though the patients reported that doctors’ explanations of the respiratory treatment were, on average, quite suitable.\textsuperscript{101} Data from the Towards a Revolution in COPD Health study demonstrate that poor adherence to inhaled therapy is more frequent in patients with poorer HRQoL and is associated with increased risk of exacerbations and mortality.\textsuperscript{102} Nonadherence is a multidetermined problem caused by, among others factors, the patient–provider relationship, the complexity of the therapy, the immediacy of beneficial effects, and patient education and knowledge of the disease.\textsuperscript{103} Inherent in the definition of “compliance” is the idea that patients are passive, acquiescent recipients of expert medical advice with which they should comply. For this reason, some authors prefer the term “adherence,” which reflects a more active patient role in consenting to and following prescribed treatments; more recently, the term “concordance” has been used to describe the “therapeutic alliance” that exists between patients and health care professionals. Pharmacological therapy of COPD is largely based in inhaled therapy, and therefore correct education and training in inhaler devices is essential to ensure compliance. Strategies to enhance adherence include simplifying the dose, choosing the inhaler device on the basis of patient characteristics, involving caregivers or family members as a useful support to care, providing information in both written and verbal forms, and establishing a good patient–physician relationship.\textsuperscript{104}

**Telehealthcare management**

Telehealthcare is the provision of personalized health care over a distance. It has three essential components: (1) the patient provides data about the illness (symptoms, oxygen saturation, sputum); (2) information is transferred electronically to a health care professional at a second location; and (3) the health care professional uses clinical skills and judgment to provide personalized feedback to the patient.\textsuperscript{105} Although telehealthcare theoretically should improve HRQoL and reduce hospital admissions by allowing early detection of exacerbations and by involving patients in self-management of the disease, study results are controversial. A systematic review of nine published studies showed that telehealthcare was effective in reducing the length of stay in hospital and emergency department visits by 21% but found a nonsignificantly increased death rate (hazard ratio = 1.21; 95% CI = 0.84–1.75) in the telephone-support group compared with the usual-care group, nor was there a significant difference in QoL or patient satisfaction with the service between the two groups.\textsuperscript{106} Similar results showing a decrease in hospital admission rates and in the total number of exacerbations without significant changes in HRQoL were reported by Trappenburg et al.\textsuperscript{107} In a recent Cochrane review, telehealthcare was associated with a clinically significant increase in HRQoL and a significant reduction in emergency department attendance and hospitalizations, without differences in 1-year survival.\textsuperscript{108} Some authors suggest that telehealthcare could reduce HRQoL and psychological well-being owing to the increased burden of self-monitoring, concerns about intrusive surveillance, a perceived lack of user-friendliness, and the undermining of the traditional (face-to-face) therapeutic relationship. The effects of telehealthcare might not be uniform across all patients, and analyses may suggest subgroups of patients for whom telehealthcare is either particularly beneficial or harmful.\textsuperscript{109,110}

**Other therapies**

In some studies, cognitive behavioral therapy – a structured psychological intervention in which the patient works collaboratively with the therapist to identify the types and effects of thoughts, beliefs, and interpretations on current symptoms, feeling states and/or problem areas – achieved improvements in QoL, anxiety, depression, and control of panic attacks.\textsuperscript{71,111,112} Similarly, relaxation therapy improved dyspnea and psychological well-being.\textsuperscript{113}

**Conclusion**

In addition to drug treatment, several nonpharmacological therapies have been shown to be useful in improving symptoms and QoL in patients with COPD. These measures may be especially useful in the management of patients with COPD and multiple comorbidities, which also may require an adaptation of the model of care to avoid fragmentation of attention among multiple specialists. Prevention of disability, malnutrition, or exacerbations, alongside the treatment of depression and comorbidities, smoking cessation, and increase in physical activity, among other measures, have been associated with HRQoL improvement. A more multidisciplinary approach and individualization of these interventions is crucial in the management of COPD patients.

**Disclosure**

The authors report no conflicts of interest in this work.
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