

STATE-OF-THE-ART REVIEW ON IMPROVING TREATMENT ADHERENCE IN COPD BY TARGETING CONCURRENT PSYCHOLOGICAL SYMPTOMS

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Abstract

Chronic obstructive pulmonary disease (COPD), a condition with significant global impact, is characterised by progressive limitation of airflow, impaired lung structure and persistent respiratory symptoms. Anxiety and depression are the most common mental disorders in COPD patients and are associated with lesser treatment adherence. We conducted a literature search on PubMed, Cochrane Central Register of Controlled Trials, Web of Science and Scopus, up to July 1, 2022, regarding COPD anxiety and depression concurrence, an underlying mechanism such as hypoxemia, smoking, systemic inflammation and finally regarding pharmacological and alternative interventions that can raise treatment adherence of COPD patients through improving psychological outcomes. Acute dyspnoea, low body mass index, female gender, poor lung function, poor performance and regular smoking are risk factors for the association between depression and COPD. Pulmonary rehabilitation and telerehabilitation increase exercise tolerance and improve the mental status and patient-related outcomes. Psychotherapy and respiratory recovery significantly alleviate symptoms and increase the quality of life. Although more research is needed, immersive virtual reality facilitated interventions reveal promising results. Improving COPD patients' treatment adherence should target concurrent psychological symptoms such as anxiety and depression.

Rezumat

Boala pulmonară obstructivă cronică (BPOC), o afecțiune cu impact global semnificativ, se caracterizează prin limitarea progresivă a fluxului de aer, afectarea structurii pulmonare și simptome respiratorii persistente. Anxietatea și depresia sunt cele mai frecvente tulburări mentale la pacienții cu BPOC și sunt asociate cu o aderență mai scăzută la tratament. Am efectuat o căutare a literaturii pe PubMed, Cochrane Central Register of Controlled Trials, Web of Science și Scopus, până la 1 iulie 2022, în ceea ce privește concurența anxietății și depresiei BPOC, un mecanism de bază cum ar fi hipoxemia, fumatul, inflamația sistemică și în sfârșit, în ceea ce privește intervențiile farmacologice și alternative care pot crește aderența la tratament a pacienților cu BPOC prin îmbunătățirea rezultatelor psihologice. Dispneea acută, indicele de masă corporală scăzut, sexul feminin, funcționarea pulmonară slabă, performanța slabă și fumatul regulat sunt factori de risc pentru asocierea dintre depresie și BPOC. Reabilitarea pulmonară și telereabilitarea cresc toleranța la efort și îmbunătățesc starea mentală și rezultatele legate de pacient. Psihoterapia și recuperarea respiratorie atenuează semnificativ simptomele și măresc calitatea vieții. Intervențiile facilitate de realitatea virtuală imersivă relevă rezultate promițătoare. Îmbunătățirea aderenței la tratament pentru pacienții cu BPOC ar trebui să vizeze simptomele psihologice concomitente, cum ar fi anxietatea și depresia.

Keywords: COPD, treatment adherence, mental health, rehabilitation

Introduction

Chronic obstructive pulmonary disease (COPD) is a common condition currently the third leading cause

of death worldwide. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is characterised by progressive airflow limitation and persistent respiratory symptoms [25]. The most

common symptoms are progressive dyspnoea and chronic cough, with or without sputum production.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) considers assessment and therapeutic targeting of depression and anxiety as one of the core principles of COPD treatment [5].

Concurrent untreated anxiety and depression impair treatment adherence in COPD patients, increasing morbidity and rate of exacerbation and the burden on healthcare providers [45].

The prevalence of COPD has an upward trend due to two main problems: exposure to risk factors and an ageing population. According to the Global Burden of Disease Study, in 2016, 251 million patients with this condition were reported worldwide [15, 43, 83]. Blanco *et al.* [8] analysed in 2018 a number of 62 studies from 19 countries and observed that the global mean prevalence of COPD is 12.38% (± 6.2), and the majority of COPD in Romania is between 10% and 15%.

The interaction between environmental factors and genetics influences the onset of COPD. COPD mainly affects people with low socio-economic status, impacting lung growth and development. Although cigarette smoking is considered the leading risk factor, the development and evolution of the disease incriminated many factors, such as other types of smoking (pipe, water pipe, cigar) [3, 27, 55, 74], exposure to respiratory pollutants, biomass fuels, air pollution, occupational exposure to organic and inorganic dust, chemical agents and vapours, abnormal lung development, accelerated ageing [20, 52]. Tobacco use can lead to underdiagnoses of COPD due to inadequate reporting of symptoms by patients, the initial signs of COPD being confused with those of excessive smoking. Maternal smoking during pregnancy is a risk factor for the foetus's lung development [25, 36, 37].

Pathophysiological phenomena such as chronic hypoxemia and systemic inflammation contribute to the associated developing conditions over time. The coexistence of COPD with other chronic diseases worsens prognosis, decreases the quality of life and increases hospitalisation costs. About 98% of patients have at least two comorbidities. Cardiovascular diseases, metabolic diseases, sleep disorders, respiratory infections, lung cancer, and psychological disorders (depression, anxiety) are the most critical comorbidities [17, 62].

Materials and Methods

We researched literature on the following databases: PubMed, Cochrane Central Register of Controlled Trials, Web of Science and Scopus, up to the first of July 2022. The search was split into three main directions: first, we searched randomised control trials involving COPD patients with concurrent anxiety and depression. Secondly, we explored the underlying mechanisms of concurrence and interdependence

between depression and anxiety in COPD through the relationship between smoking, systemic inflammation and chronic hypoxemia; thirdly, we searched the gold standard pharmacological and also alternative treatments to improve quality of life and adherence by targeting psychological symptoms such as pulmonary rehabilitation, telerehabilitation, psychotherapy and digitally delivered interventions such as immersive virtual reality, to reflect the state of the art of the perspective we assessed.

Anxiety and depression in COPD

Depression in the COPD patient is often underdiagnosed, influences the prognosis, increases the rate of exacerbations and decreases treatment compliance. The prevalence of depression in COPD varies in different studies, but it has been found that the majority of depression, anxiety and COPD increase with the severity of COPD. In a prospective longitudinal study of 355 COPD patients, Blakemore *et al.* [7] showed that a mild form of depression doubles the number of visits of COPD patients to an emergency department, while moderate to severe conditions of depression lead to an increase in the rate of visits to an emergency department up to 5 times.

Studies [38, 51] mention that anxiety and depression are more common in women with COPD compared to men with COPD. In a prospective study that included 202 patients with COPD, di Marco *et al.* [18] investigated the prevalence of depression and possible differences in clinical and functional parameters by gender. The results of the study showed a high prevalence of depression and a more severe degree of dyspnoea in females ($r = 0.541$, $p < 0.001$) compared to males ($r = 0.211$, $p < 0.05$). Lee *et al.* [39] also report that patients who are alone (OR 1.86, 95% CI, 1.37 - 2.51, $p < 0.01$) and who have a poor socio-economic status (OR, 2.17; 95% CI, 1.55 - 3.04, $p < 0.01$) have an increased risk of developing depression in the early stages of COPD.

Patients with COPD and depression have decreased self-care and low quality of life due to multiple bacterial, viral or fungal infections exacerbations. Also, these patients have more hospitalisations and more hospitalisation days. Studies show an increase in the number of visits to the emergency department for smokers compared to non-smokers [7]. Depression potentiates the effects of certain COPD disorders. For example, patients with depression and COPD are more likely to experience sleep disorders. Those with long-term oxygen therapy at home have poor adherence to therapeutic management and even refuse resuscitation during cardiopulmonary arrest [82].

It is difficult to diagnose depression in the patient with COPD due to the overlapping of similar symptoms: impaired sleep quality, impaired appetite, difficulty concentrating, functional disorders, and, in the

management of exacerbations of the disease marked as asthenia [72]. With the progression of COPD, recognising depressive symptoms (Figure 1) becomes more and more complex, with patients experiencing somatic symptoms such as weight loss and muscle loss, crying easily and social isolation. On the other hand, COPD is considered a disease of the elderly, so we can say that ageing is crucial in developing depressive symptoms in patients with COPD [1, 56, 68].

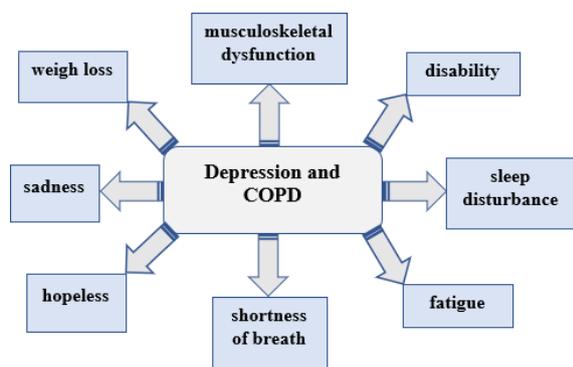


Figure 1.

Clinical characteristics of patients with COPD and depression

Factors influencing the prognosis and quality of life of patients with COPD and depression

Sleep disorders

Patients with COPD and depression often have sleep disorders that decrease their quality of life. Restless sleep increases COPD exacerbations and higher mortality rates. Polysomnography results show that women have frequent awakenings during the night compared to men. Severe disease forms associated with severe dyspnoea and nocturnal desaturation are more prone to fragmented sleep [69]. Chronic insomnia also aggravates depressive syndrome and negatively influences social adjustment. Sleep apnoea syndrome is a common cause of insomnia and daytime sleepiness in patients with COPD-depression concomitance and can lead to cardiovascular complications. The first therapeutic

measure, in this case, is sleep hygiene which involves a healthy lifestyle, avoiding heavy meals, tobacco and drinking alcohol and caffeine in the evening, at least 4 hours before bedtime. Practising physical exercises improves prognosis and mental status and increases exercise tolerance [11]. Daytime sleepiness affects the ability to concentrate and memorise and increases the risk of road accidents and accidents at work and home [59].

Chronic hypoxemia

One of the pathophysiological phenomena of COPD is hypoxemia, which must be evaluated and treated. It is necessary to improve the patient’s hypoxemia during an exacerbation by supplementation with oxygen and to maintain saturation above 88% [25]. Many studies have shown that the severity of hypoxemia in COPD is directly proportional to the degree of impairment of ventilatory function. Over time, chronic hypoxemia leads to comorbidities such as pulmonary hypertension, secondary polycythaemia, depressive syndrome and the development of systemic inflammation [68]. Intermittent hypoxemia may be commonly seen in patients with sleep apnoea, but hypoxemia may occur during exertion or sleep in the COPD-depression coexistence. Patients with COPD and sleep apnoea have an increased tendency to develop depression [34]. Although initially, oxygen saturation is low during the night, in the COPD-sleep apnoea combination, the onset of hypoxemia is also favoured during the day. Ageing is a keyword in developing depressive symptoms in COPD patients [1, 50].

COPD Assessment Test (CAT) is a symptom assessment questionnaire specific to COPD and contains eight items, graded from 0 to 5 points, totalling a maximum of 40 points. The final score falls into one of the ranges: 0 - 10 (mild clinical impact), 11 - 20 (moderate clinical impact), 21 - 30 (severe clinical impact) and 31 - 40 (very severe clinical impact) [77]. The usefulness of the CAT score in patients with depression and COPD has been investigated by multiple authors (Table I).

Table I

Summarises the CAT score results in patients with COPD and depression

Study, year	Subjects, n	GOLD stages	CAT score (mean ± SD)
Lee <i>et al.</i> , 2013 [40]	191	I, II, III, IV	16.2 ± 8.4
Nowak <i>et al.</i> , 2014 [49]	29	I, II, III, IV	17.4 ± 7.4
Chen <i>et al.</i> , 2015 [14]	35	I, II III, IV	17.14 ± 6.1 27.46 ± 10.06
Yao <i>et al.</i> , 2020 [84]	65	I, II, III, IV	13.08 ± 3.71
Long <i>et al.</i> , 2020 [41]	195	I, II, III, IV	24.5 ± 8.0

Data are presented as mean ± standard deviation or number.

Lee *et al.* [40] support the usefulness of performing the CAT test for depression screening in COPD. According to the study [61], a high CAT score (≥ 21) increases the probability of developing depressive syndrome (80.6% accuracy). Silva Júnior *et al.* [61]

mention the usefulness of the CAT score in diagnosing the major depressive disorder in patients with COPD and mild hypoxemia. Assuming that patients with depression have a high CAT score, 30 patients with major depression and 30 patients without depression

were included. For the diagnosis of major depression, a psychiatric evaluation and Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria were required. All patients included in the study were over 40 years of age and had, as a primary diagnosis, stable COPD with mild hypoxemia. The study showed that a CAT score above 20 is associated with significant depression. Thus, the CAT score can be used as a predictor in diagnosing major depression in COPD patients with mild hypoxemia.

Smoking

Smoking, the leading risk factor for COPD, is often associated with depression and anxiety. Thus, smoking, COPD and depression are closely linked. Atlantis *et al.* [2] state that the association between depression and anxiety in COPD is bidirectional, with smoking being considered a bridge between the two conditions. Depression plays a role in initiating and maintaining smoking; smoking frequently leads to the development of COPD, and COPD, in turn, contributes to the onset and worsening of depression and anxiety [26, 44].

In a prospective study, Lou *et al.* [42] mention that smoking, depression and anxiety increase mortality in COPD patients. The study included 7787 COPD patients and showed that smoking status and depression influence the prognosis of COPD. Thus, current smokers and former smokers with depression have a higher mortality rate compared to those who have never smoked [18].

Some studies have investigated the link between depression and social smoking, also called intermittent smoking. Rocha *et al.* [57] showed in a survey of a population of 1054 people over the age of 40 that depressive symptoms frequently occur in people who smoke occasionally. In a prospective study, Bonilha *et al.* [9] investigated the effects and benefits of smoking among adolescents. Two questionnaires were used, the University of São Paulo Reasons for Smoking Scale (USP-RSS) and the Fagerström Test for Nicotine Dependence. The study's results showed that most adolescents (90.2%) had low values of the Fagerström test (social smoking), which correlated with depressive symptoms. The ECLIPSE study (prospective observational study), conducted over three years in 46 centres in 12 countries, enrolled 2118 subjects with COPD, 335 issues without COPD and 243 non-smokers without COPD. Among subjects with COPD, an increased prevalence of depression was recorded in the following categories: women, active smokers and those with severe COPD and comorbidities. The study also showed a 30% decrease in mortality in COPD patients who resorted to a mental health specialist compared to those who resorted to health care, but not to a specialist [28].

Systemic inflammation

Systemic and pulmonary inflammation plays a vital role in the development and progression of COPD. Comorbidities associated with the disease and inflammatory

status are adverse prognostic factors in the evolution of COPD. In recent years, the role of proinflammatory cytokines in both COPD and the depressive syndrome has been increasingly studied. Thus, it was found that the following mediators are involved in the pathogenesis of the two diseases: interleukin-1 α (IL-1 α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumour necrosis factor α (TNF- α) [16]. Because TNF- α plays an essential role in lung inflammation, inhibiting TNF- α can be used as a marker in inflammatory diseases. The underlying mechanism of systemic inflammation is an increase in proinflammatory cytokines (IL-1 α , IL-1 β , IL-6) and a decrease in anti-inflammatory cytokines, such as IL-10 [6, 32, 48]. Increased values of high-sensitivity C-reactive protein and fibrinogen are markers of inflammation in depression and COPD. A high C-reactive protein (CRP) value in the peripheral blood is also found in other pathologies, such as cardiovascular or metabolic disorders. Some studies point to a correlation between increased CRP and inflammation in the brain, but more studies are needed. Other studies suggest that elevated CRP may be used, on the one hand, as a marker of predictability in the development of depressive syndrome; on the other hand, a high CRP value may be associated with resistance to antidepressant treatment [22].

In depression, cytokines act on synaptic neurotransmitters, serotonin, norepinephrine, dopamine, and amino acid metabolism. The primary amino acids involved are tyrosine, tryptophan, phenylalanine and glutamate [4, 23]. Among the cytokines involved in the chronic inflammatory process in COPD, Kleniewska *et al.* [35] mention IL-1 β , IL-6 and TNF- α , which show increased values in induced sputum.

Previous studies have looked at the link between COPD, depression and IL-6 and found that there are changes at the molecular level. As IL-6 is released through kynurenine, which is involved in serotonin homeostasis, systemic inflammation and depression, there is an increase in IL-6 and a low level of serotonin [67]. Both in COPD and depression, IFN- γ and IL-2 were found to be involved in the inflammatory process. Thus, in COPD, inflammation is closely related to the presence of T lymphocytes, most of which are CD8⁺ cells, but CD4⁺ cells are also present. Uzeloto *et al.* [75] showed in a study that high CD4 + IL-2 correlates with acute bronchial obstruction.

BODE index (Body mass index, airflow Obstruction quantified by FEV1 ((Forced Expiratory Volume in the first second), dyspnoea quantified by mMRC scale (modified Medical Research Council)), exercise tolerance evaluated by 6MWT (6-min Walk Test) assesses the clinical and functional status of COPD patients. It is a good predictor of death risk. Meshram *et al.* [46] investigated the relationship between markers of inflammation, such as CRP, IL-6, TNF-alpha, LDH, cortisol and the BODE index, in a case-control study; 50 patients with stable COPD and 50 healthy people

were included. The study showed a positive correlation between IL-6 and the BODE index in the group of patients with COPD. A directly proportional increase was also found between IL-6 and the BODE index; as IL-6 increases, so does the BODE index.

Figure 2 shows the consequences of risk factors in patients with COPD and depression.

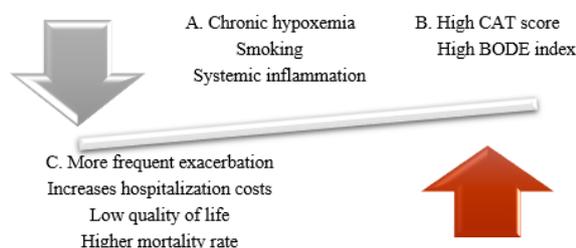


Figure 2.

The balance between risk factors and the consequences of the association of depression in the COPD patient

- A. General risk factors; B. Individual risk factors;
C. Consequences

Current therapies targeting psychological aspects of COPD

Pharmacological treatment

COPD patients who also have depression can receive the recommendation for antidepressant treatment. Speciality guidelines indicate the prescription of serotonergic antidepressants (selective serotonin reuptake inhibitors (SSRIs) or serotonin–noradrenaline reuptake inhibitors (SNRIs)) for moderate-severe forms of depression. Serotonergic antidepressants bring additional benefits compared to tricyclic antidepressants; they present fewer adverse effects, and their use is safer. A retrospective cohort study showed the importance of antidepressant treatment in newly diagnosed COPD patients. The study included 25,458 patients with COPD and depression, of whom 82% were on antidepressant therapy.

The results showed that treating depression increased adherence to pharmacological treatment for COPD and improved prognosis [81].

Pulmonary rehabilitation

Progressive deterioration of symptoms is an indication of pulmonary rehabilitation. According to the European Society of Respiratory Diseases guide, pulmonary rehabilitation is a non-pharmacological intervention. It involves a thorough assessment of the patient, followed by a therapy tailored to each patient, which includes physical training, nutritional counselling and education. These objectives have a role in reintegrating into society and regaining autonomy. Multiple studies have shown that, in the COPD–depression combination, pulmonary rehabilitation and exercise influence the prognosis, improve symptoms, reduce dyspnoea and improve mental state. To benefit from pulmonary rehabilitation, the individual must attend a program in specialised medical centres or at home under the

guidance and supervision of a specialist [12, 53, 65, 85].

Respiratory control is one of the components of pulmonary rehabilitation with proven effectiveness in reducing depression, dyspnoea and efficient oxygenation of the muscles involved in respiration. Another goal of pulmonary rehabilitation is emotion management. Patients with COPD and depression may benefit from individual or group psychotherapy, relaxation therapies and stress management methods [85].

The TANDEM program aimed to promote pulmonary rehabilitation in patients with COPD and depression, thus reducing symptoms in this category of patients. The program advanced various techniques for managing dyspnoea, increasing the level of physical activity and decreasing the degree of social isolation. Individual sessions were carried out with patients who met the inclusion criteria. These sessions took place weekly, between 40 and 60 minutes, for 6 to 8 weeks, depending on the severity of the symptoms characteristic of depression [63].

The BODE index has been used in various studies to assess the effectiveness of pulmonary rehabilitation. Although the 6-minute walk test was initially performed to evaluate exercise tolerance, multiple alternatives have been proposed, as this test cannot be performed in all care centres. Thus, the effectiveness of the 4-minute walk test was investigated. The test has been used in patients with idiopathic pulmonary fibrosis with significant results; however, further studies are needed in COPD [79]. The first study to investigate the relationship between the 4-minute walk test, the modified BODE index, and the prognosis of COPD patients was conducted by Vieira *et al.* [79]. Within the adjusted BODE index, the exercise tolerance was tested by the number of steps climbed. Patients who climbed more than 65 steps in the walk test had a better prognosis than those who climbed less than 65 steps or had desaturation ($SpO_2 \leq 90\%$). The presence of desaturation during the walk test increased the mortality rate by 2.8 times compared to those without desaturation [63, 66, 79].

Another concept studied in the COPD–depression combination is a sedentary lifestyle. Some studies report that patients with COPD and depression have an increased tendency toward low-energy activities, even preferring sedentary activities in exchange for exercise [13, 31, 64]. One solution to reducing a sedentary lifestyle is implementing light activities such as housework, walking or cycling [47]. Studies have shown that people with COPD with favourable outcomes in pulmonary rehabilitation programs were those with good mental status. Thus, in addition to the pulmonary rehabilitation program, psychotherapy is recommended [13, 33]. Farver-Vestergaard *et al.* [71] mention that patients who underwent pulmonary rehabilitation without attending mindfulness sessions had higher TNF- α values compared to patients who,

in addition to the pulmonary rehabilitation program, attended mindfulness sessions.

Telerehabilitation

The concept of telerehabilitation supports patients with COPD and depression, with similar results to classical pulmonary rehabilitation. The American Thoracic Society (ATS)/European Respiratory Society (ERS) recommend telerehabilitation to make access to programs more accessible and more and more patients to benefit from these programs [29, 30, 58]. Telerehabilitation involves monitoring by audio-video means, recording of pulmonary rehabilitation programs and remote assessment of patients. Zanaboni *et al.* [86] investigated, in a pilot study, the feasibility of long-term telerehabilitation in patients with moderate to severe COPD located in northern Norway. Subjects were trained and monitored for two years *via* video-conference by a physiotherapist.

The equipment needed to conduct the study consisted of a treadmill, pulse oximeter, tablet and a website

through which the subjects had access to training. The study positively impacted the included issues as no dropouts after one-year of training increased physical and mental performance and quality of life. Moreover, telerehabilitation has reduced hospitalisation costs by about 27%. Tsutsui *et al.* [73] studied the importance of telerehabilitation in COPD patients and patients with a history of SARS-CoV-2 virus disease. Some of them later developed conditions such as depression or anxiety. The treatment regimen of these patients included pulmonary rehabilitation performed either in the hospital or at home through the media. In the post-COVID era, the merits of telerehabilitation are substantial, but further studies are needed to implement telerehabilitation programs [78]. Several studies (Table II) have shown that telerehabilitation helped patients with COPD-depression coexistence. Control group is composed of patients who received medical therapy (they did not have an exercise program to execute).

Table II

Overview of 3 studies on the importance of pulmonary rehabilitation in the COPD depression concomitance

Study	Groups	All (n)/ women (n)	Completed, (n)	Age, years (MS)	BMI, kg/m ² (MS)	Study duration (weeks)	GOLD COPD Stage (n)				HADS (MS)	Results
							I	II	III	IV		
Hansen <i>et al.</i> [29]	PTR	67/35	57	68.4	25.5	10 (60 min x 3/week)	0	0	37	30	4.5	The PTR Group present a reduction of depressive symptoms compared with the CPR group.
	CPR	67/39	43	68.2	25.9	10 (90 min x 2/week)	0	0	45	22	4.1	
Tsai <i>et al.</i> [71]	PTR	20/7	19	73	28	8 (15 - 30 min x 3/week)	5	6	8	0	5	This study showed that telerehabilitation increased exercise tolerance and quality of life.
	CG	17/11	17	75	28	8	6	6	5	0	5	
Bourne <i>et al.</i> [10]	PTR	64/23	57	69.1	27	6	15	26	17	6	10	The two groups had similar results regarding the symptoms and the 6MWT distance.
	CPR	26/8	21	71.4	28	6	5	13	7	1	10	

PTR – pulmonary telerehabilitation; CPR – conventional pulmonary rehabilitation; CG – control group (treatment as usual); HADS – Hospital Anxiety and Depressions Scale; MS – mean score; n – number of participants

Psychotherapy techniques and the role of Immersive Virtual Reality (iVR)

Among the non-pharmacological interventions indicated in COPD and depression coexistence, the researchers proposed cognitive-behavioural therapy, which reduces the intensity of perceived anxiety and depression while improving physical and mental conditions.

Panagiotti *et al.* [51] investigated the role of cognitive-behavioural therapy (CBT) in patients with COPD and mild to moderate depression and anxiety disorders. The study showed reduced symptoms and the importance of associating CBT with exercise.

In a randomised controlled trial, Doyle *et al.* [80] report the effectiveness of cognitive-behavioural therapy performed at home through telephone calls. COPD patients usually have dyspnoea that limits their physical activity and impairs their ability to move.

Approximately 75% of patients with COPD and depression reported difficulties participating in physical therapy sessions. Telephone-based cognitive-behavioural therapy benefits patients because it involves easy access by telephone and does not impose restrictions such as space, time, or additional costs [54].

Another non-pharmacological therapy that has proven effective is mindfulness therapy. Mindfulness-based programs usually involve eight courses, group therapy, and interventions such as cognitive therapy, mindfulness-based stress reduction, meditation and other methods of mindfulness. These programs effectively improve chronic symptoms and assist people with COPD and depression in adopting a healthy lifestyle and improving their well-being [70]. Another therapy that brings benefits to patients with depression and COPD includes practising breathing techniques, focusing

on how to breathe, and adopting a positive mental status [76].

3d iVR technological breakthroughs allow for affordable access to fully immersive, personalised psychotherapy or medical environments that resemble realistic situations otherwise hard to replicate in the actual world, thus suggesting the potential to outperform conventional interventions when targeting anxiety [24]. Although iVR has been used extensively and effectively to treat post-stroke, cognitively impaired or elderly failing patients and children with motor deficits, it was only recently implemented in COPD management [80].

In terms of mood improvement and anxiety reduction, COPD patients benefit from the augmentation of pulmonary rehabilitation with iVR therapy. Although the role of iVR in COPD anxiety and depression is not yet sufficient, preliminary research shows that it might be more effective than the current gold standard of autogenic training in treating COPD patients regarding the confluent concurrence of anxiety and depression [60].

Conclusions

COPD and depression are two heterogeneous conditions that are commonly associated. COPD can be prevented and treated, but the complications associated with this disease lead to premature mortality. Depression is a common comorbidity in COPD patients and is often underdiagnosed and undertreated due to similar symptoms. Usually, the diagnosis of depression, in this case, is based on questionnaires. It is essential to diagnose and treat COPD depression as depression adversely affects the prognosis, and treating COPD depression increases the quality of life. Progressively, COPD progression impairs both subjective and objective HRQL measures.

Anxiety and depression are two of the most accurate indicators of low HRQoL and treatment adherence. Evidence suggests that fear, sadness and suicide ideation are widespread among COPD patients. There are essential links between anxiety and depression levels and decreased HRQOL, according to studies. These results imply that future COPD therapies may prioritise subjective and experiential disease correlates in addition to objective lung function.

Exposure to risk factors leads to a pulmonary and systemic inflammatory response. Chronic hypoxemia and systemic inflammation are incriminating risk factors for depression in COPD patients and should be appropriately evaluated and managed. Pulmonary rehabilitation is indicated for all patients with COPD and depression and aims to improve respiratory and mental symptoms, increase exercise tolerance, prevent associated complications and reduce hospitalisations.

To improve the physical and mental status of patients with COPD and depression, the adoption of mental health programs and pulmonary rehabilitation is

encouraged. Telerehabilitation allows transmitting information in real-time, but real-time studies are needed to highlight the benefits of this program. Relaxation or meditation techniques are effective in improving psychological support.

Pharmacological treatment is complementary to non-pharmacological treatment. Patient education, knowledge of the disease, management of symptoms and adverse drug effects help improve the prognosis of patients with COPD and depression.

iVR represents a viable alternative for pulmonary rehabilitation, although more research is needed before fully implementing this technology for treating anxiety and depression associated to COPD. Autonomous iVR facilitated interventions targeting psychological symptoms such as anxiety and depression may improve the currently impaired treatment adherence and furthermore the prognosis, decreasing COPD mortality.

Given the frequent association between COPD and psychological symptoms such as depression and anxiety, future studies are needed for screening and identifying treatment options that facilitate improved patient-reported symptoms resulting in increased treatment compliance and better quality of life.

Conflict of interest

The authors declare no conflict of interest.

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